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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 11 1955

THE EVOLUTION OF THE TREATMENT OF ADDISONIAN ANAEMIA*

BY

Sir LIONEL WHITBY, C.V.O., M.D., F.R.C.P.

Regius Professor of Physic in the University of Cambridge

The rational treatment of any disease is governed entirely by the depth of understanding of its fundamental cause and of the factors which may contribute. The treatment of Addisonian anaemia has therefore evolved with the accumulation of knowledge through the century since 1855, when Addison, in the preamble to his classical monograph, *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*, wrote his few brief paragraphs on an "idiopathic anaemia."

It would not be within the terms of my title to enter into a long discussion on whether the first recognizable clinical descriptions of Addisonian anaemia should be ascribed to James Scarth Combe, of Edinburgh, to Thomas Addison, of Guy's, or to Professor Anton Biermer, of Zurich. But it would be appropriate to mention that Addison recognized that the malady was fatal, the onset was insidious, the usual symptoms of anaemia were present, that the body fat was often well preserved, and that treatment was ineffective. He stated that the condition arose from "no discoverable cause whatever," but speculated that "from the disease having uniformly occurred in fat people" he was "naturally led to entertain a suspicion that some form of fatty degeneration might have a share at least in its production."

Addison's most clear description—though submerged in his classical monograph on suprarenal disease, and consequently open to the criticism that the author was confusing two diseases—is nevertheless far superior to that given by Combe (1824), whose patient had, indeed, a severe anaemia, but with no convincing features suggestive of Addisonian anaemia.

There is no doubt, however, that the account of 15 cases of fatal anaemia which he had met with in the course of five years, given by Biermer in 1872, came nearer than any other that had previously appeared to depicting Addisonian anaemia as it is recognized to-day.

Addison's position was, however, firmly established some years after his death by two staunch advocates: first, his devoted pupil—Samuel Wilks—who in 1874, in a letter to the *British Medical Journal*, asserted that Thomas Addison had lectured about the disease as far back as 1843; and, secondly, William Pepper, professor of clinical medicine in the University of Pennsylvania, himself greatly interested in the disease, who gave, in 1875, some of the first reports of the bone marrow—albeit not very convincing, since they suggest leukaemia rather than pernicious anaemia—and who considered that "the older and equally clear description by Addison of idiopathic anaemia was one and the same affection as the progressive pernicious anaemia reported by Biermer."

Addison as a Diagnostician

Addison was outstandingly famous as a diagnostician; his obituary notice in the *Medical Times and Gazette* (1860, **2**, 20) says: "Diagnosis was his *forte*, and those who knew him best are aware that he stood unrivalled in his power of searching into the complex framework of the body and dragging the hidden malady to light. His very meagre and simple prescriptions—if he remembered to prescribe at all—showed that he made no study of therapeutics."

Nevertheless, in what is always regarded as his first public pronouncement on Addisonian anaemia, his communication to the South London Medical Society in 1849, there are some scant descriptions of treatment, but it is difficult to know whether Addison was then speaking of suprarenal disease or his "idiopathic anaemia." The probability is the former, but there is clearly confusion of both. Whatever may have been the nature of these cases, the somewhat non-specific treatment can be regarded as appropriate to all of them.

In referring to two patients who recovered, he says of one, "A man below the middle period of life, who was looked upon as past all hope, and suspected to be suffering from some latent malignant disease, slowly, but steadily, recovered under the free use of brandy, but with the singular result that the hair on one side of his head turned permanently grey, whilst the other side retained its original brown colour."

Treatment of anaemia at that time had not progressed since the time when Sydenham wrote, "We give Mars in the pale colours, the pallor disappears, and once again the face is rosy and ruddy." Then, as now, the iron-deficiency anaemias would have responded to iron in the form of the oxide, the sulphate, and the carbonate, provided sufficient was given, and this irrespective of mercury and other metals, the astringents, diet according to the powers of the stomach, as well as formidable purgings, which were put into operation at the same time.

Pepper (1875), however, appreciated that Addisonian anaemia was in a class by itself, and doubtless he had found, like others, that iron was ineffective. Unhampered by our modern knowledge of such trivialities

*Addison Centenary Memorial Lecture delivered at Guy's Hospital Medical School on March 23, 1955.

as blood groups, he made at least a rational if somewhat perilous approach to symptomatic treatment by advocating and practising blood transfusion, with reactions and results which strike terror into the heart of the modern reader.

Approach to Rational Treatment

At this time—the 'seventies—the current views on aetiology can hardly be regarded as pointing the way to rational treatment, but even then the possibility of a psychosomatic influence was being seriously considered.

Samuel Wilks (1874), in the letter to which I have already alluded, and in which he succinctly established the priority of Addison over Biermer, said: "I express an opinion that nervous shock may be the starting point of the morbid process, and I know of a case where a young lady poisoned her father, and was so overwhelmed with grief that she took to her bed, became anaemic and died. Two of my cases gave a distinct history of moral shock, and a young lad, who died in one of Sir W. Gull's beds, with extreme anaemia, had never been well since he had been attacked by a sheep in a field." He then delivers the knock-out blow to the Continental claim: "The German and the Swiss doctors do not allude to this probable cause."

The last quarter of the nineteenth century provided a steady accumulation of clinical detail about Addisonian anaemia, but relatively little in the way of fundamental understanding, with the one exception of the finding of changes in the stomach, which, however, were not properly comprehended at that time. Consequently, though the clinical entity itself became clearer, the approach to rational and specific treatment was wanting. Glossitis, a number of characteristic changes in the peripheral blood, the hereditary factor, retinal haemorrhages, and neurological changes all came to be built into the picture of the disease.

It was Samuel Fenwick (1877), physician to the London Hospital, who supplied the first appreciation of the importance of stomach function. In a lecture on "Atrophy of the Stomach" he made a clear distinction between Addison's anaemia and Addison's disease, and he described four cases of the former which, after death, had a well-marked lesion of the glandular structure of the stomach. He says: "The stomach showed no signs of post-mortem solution; the whole of the glandular structure of the organ was in a state of atrophy." He actually tested an infusion of the stomach with half a drachm of hydrochloric acid for its power to digest hard-boiled egg. This observation—the failure of stomach function—was, as we now know, the key not only to the proper understanding of the disease but also to its specific treatment as practised to-day.

However, the correct interpretation of these findings was side-tracked—in fact, obscured—for almost half a century after Samuel Fenwick's lecture, largely as the result of the work of William Hunter (1901), a physician at Charing Cross Hospital, who in an incisive and convincing monograph postulated a septic origin for the disease.

A Septic Origin?

Hunter's thesis was based on the belief that Addisonian anaemia was essentially haemolytic by reason of infection of the alimentary canal with haemolytic organisms. The preface to his monograph contains a table in the form of a genealogical tree emanating from the question "What is Pernicious Anaemia?" and evolving to be answered in the later "generations" by confident statements that the disease must originate in the gastro-intestinal area from a "special poison" in the liver, from "infection" in the intestine and stomach, the latter with *Streptococcus longus*, and a "special infection" with associated dental cario-necrosis and glossitis.

Hunter's monograph, convincingly written, greatly influenced the treatment of Addisonian anaemia. First, he advocated the prevention and removal of the infective cause of the disease by paying attention to the hygiene of the teeth and of the mouth. Secondly, he said it was essential to change such conditions in the gastro-intestinal tract as favoured the operation of the infective cause. This was done by washing out the stomach, by administering what was regarded as a gastric antiseptic—salicylic acid or bismuth salicylate—as well as intestinal antiseptics, such as salol, naphthol, calomel, or mercuric chloride, and, not least, enemata containing salicylic acid. Thirdly, there were certain measures designed to combat the chief symptoms, of which the most important and most widely used was arsenic in the form of Fowler's solution. This had been introduced by Byrom Bramwell (1877), with high hopes of effecting permanent cure, though experience had shown that it had only a temporary beneficial influence.

It is perhaps interesting to note that Minot and Castle (1935) took the trouble to investigate the action of arsenic in pernicious anaemia when they were carrying out their studies on the significance and interpretation of the reticulocyte count. They found that arsenic would produce an irregular and often sustained reticulocyte response in pernicious anaemia, sometimes associated with showers of nucleated cells, but that the reaction was not physiological, since any subsequent rise in the red-cell count, if such occurred at all, was irregular, disorderly, and incalculable. It is now known that arsenic has no real blood-building value and that it acts as a bone-marrow depressant rather than as a stimulant.

Hunter also practised dietetic treatment, stating as his view that "the most important factor regulating the amount of blood destruction in health is the nature of the diet, a nitrogenous diet causing a much greater destruction than a farinaceous one." He also made a very limited trial of antistreptococcal serum, but even though most of the cases which he records seem to have had a remission he clearly rated this remedy quite low.

Hunter's views dominated the treatment of pernicious anaemia for a quarter of a century, and were supported by Arthur Hurst (1923), who showed that, as the result of oral sepsis, the *Str. longus* became implanted in, and could be recovered from, both stomach and duodenum. Hurst is best known for his emphasis upon the loss of stomach function, particularly the complete achlorhydria so characteristic of Addisonian anaemia, which permitted the implantation of the toxin-producing streptococcus in the upper part of the alimentary tract. Hurst realized the primary importance of the achlorhydria, since it preceded the anaemia and was not, therefore, a secondary phenomenon, whilst it persisted even in remission. He held the view that the anaemia and nervous system changes were both toxic in origin.

When I entered the wards of the Middlesex Hospital in the early 'twenties, the main treatment of Addisonian anaemia followed the views of William Hunter, as expanded by Hurst. Wholesale dental extractions, the administration of arsenic, dilute hydrochloric acid three times a day before meals, for life, together with acidophilus milk. Splenectomy had also a considerable vogue, especially following the reasonably favourable report of Krumbhaar (1916).

Transfusion, with or without splenectomy, was also widely practised, especially in America, with, however, no more than a temporary effect, and this method of treatment must have given George Minot (Minot and Lee, 1917) some of his first experience with pernicious anaemia.

The Work of Whipple, Minot, and Murphy

Meanwhile, in the year following the first world war the way was being prepared for one of the most far-reaching discoveries in medicine. As early as 1918, George Whipple, first in California, and later in Rochester, began a long-term fundamental study upon the power of different foodstuffs—meat, liver, and other substances—to effect the regeneration of haemoglobin in dogs, otherwise maintained on a

standard basic diet, and exsanguinated to a fixed degree. This original and ingenious programme was both simple and effective.

During the period from 1918 to 1925, in association with his colleagues C. W. Hooper and Mrs. Robscheit-Robbins, Whipple published a series of papers, unravelling the basic physiology of haemopoiesis in a systematic and orderly manner, and with a thoroughness and pertinacity which can scarcely have been equalled before or since. The most significant papers in relation to my theme are entitled: "Blood Regeneration following Simple Anaemia: Influence of Meat, Liver and Various Extracts Alone or Combined with Standard Diets" (Hooper, Robscheit, and Whipple, 1920); "Favourable Influence of Liver, Heart, and Skeletal Muscle in Diet on Blood Regeneration in Anaemia" (Whipple and Robscheit-Robbins, 1925). It should also be noted that Whipple (1922) had suggested that, "In pernicious anaemia, there may be a scarcity of the material from which the stroma of the red-blood cells are formed or that a disease of the stroma-forming cells of the marrow exists."

Critics have sometimes said that though Whipple and his colleagues clearly demonstrated the virtues of liver and other substances in blood regeneration, their standard of reference, a dog rendered anaemic by bleeding, bore no resemblance whatever to pernicious anaemia. But no one can read the first fully documented paper of Minot and Murphy (1926) without feeling Whipple's influence, and, indeed, the paper contains this significant paragraph: "Following the work of Whipple and Robscheit-Robbins, we made a few observations on patients, concerning the influence of a diet containing an abundance of liver and muscle-meat, on blood regeneration. The effect appeared to be quite similar to that which they obtained in dogs. These observations, together with the information given above, led us to investigate the value of a diet with an abundance of food rich in complete proteins and iron—particularly liver—and relatively low in fat, as a means of treatment for pernicious anaemia."

The award of the Nobel Prize in 1934 to Whipple, Minot, and Murphy expressed the judgment of an impartial world towards these great men.

Looking back over the intervening period and re-reading Minot and Murphy's simple conclusion that "the dietetic treatment of pernicious anaemia is of more importance than hitherto recognized," one must greatly admire their modesty and the care with which they attempted to control their remarkable results. Their most commendable caution in interpreting therapeutic successes in a disease well known to be subject to one or more spontaneous remissions ought to be blazoned as an example to all who undertake therapeutic trials. After a most critical discussion of results with other remedies, they say, in relation to the obvious constancy and endurance of their own: "There is no data to indicate whether the remission in these 45 cases will last longer than those of others." This simple paper, patently honest and diffident in the extreme, resembles the gentle opening bars of a great unfinished symphony, of which some movements have even now not yet been composed, much less played.

A Developmental Sequence

The developments have been remarkable: In therapeutics, the sequence from liver itself to oral and parenteral extracts, crude and refined, to folic acid, folinic acid, and vitamin B_{12}. In clinical medicine, the comprehension of much about the megaloblastic anaemias—not only pernicious anaemia, but also the nutritional anaemias of pregnancy, infancy, and alimentary disturbances such as sprue. In physiology and pathology, a steady advance in knowledge of the fundamental processes of blood formation, including the cytochemistry and biochemistry of erythropoietic metabolism, all of which has illuminated the field of protein chemistry far beyond the haemopoietic system.

With the discovery of the efficacy of liver the true pathology and aetiology of Addisonian anaemia was shown to be not a haemolytic phenomenon but a maturation defect causing dyshaemopoiesis—a shift from a destructive process to a deficiency disease. Nevertheless, there is ample evidence that excessive red-cell destruction contributes to the anaemic state, even though this haemolytic aspect is of quite secondary importance compared with dyshaemopoiesis (Singer *et al.*, 1948).

The concept of Addisonian anaemia has, however, been greatly extended, so that it is now regarded as a generalized cellular disease, and not simply as a dyshaemopoietic anaemia with neurotrophic complications. Cellular degenerations or changes are found not only in the erythroblasts of the bone marrow and the tissue of the central nervous system, but also in the granular leucocytes of the marrow giving rise to macropolycytes, in the megakaryocytes, in the epithelial cells of the tongue, oesophagus, stomach, and even the respiratory tract (Graham and Rheault, 1954). These multiple changes are all rectified with liver or vitamin B_{12}.

Many times during the past hundred years has diet been considered important in the treatment of Addisonian anaemia. Many times also has the fashion changed, as is so frequently the case with dietetic measures for any pathological condition even to this day. Fenwick (1880), for example, recommended protein foods rather than farinaceous, whereas Hunter advocated the reverse. It should also be appreciated that others (Gibson and Howard, 1923) before Minot and Murphy—some also basing their work on that of Whipple and his colleagues—had prescribed liver for patients with Addisonian anaemia, and had reported improvement, but none had recognized that liver possessed a complete curative effect.

What is remarkable is not that Minot and Murphy thought of trying the effect of liver, since there were a number of pointers, from the well-known beneficial effect of liver-soup in sprue to the experimental work of Whipple, but that they had the foresight or instinct or courage to exhibit it in sufficient amount—half a pound or more of raw or lightly cooked liver a day for life—and with sufficient persistence to obtain and maintain the required effect.

There should be a plaque somewhere to record the fortitude and faith of the first 45 patients with Addisonian anaemia whom Minot and Murphy treated, who endured this nauseating treatment and so gave this great boon to mankind.

When I was in Boston in 1946 there was a dramatic clinical demonstration of two cases of Addisonian anaemia at the Peter Bent Brigham Hospital. Minot and Murphy were both present. The first case was one of the original series of 45 reported in 1926; the patient, a woman, had reached the age of 80, and was dying of carcinoma of the stomach; she had had more than twenty years of happy life, and had graduated through all the advances in liver therapy to that time. The second case, a newly identified one, presented as a contrast, had, with one single parenteral injection of a concentrated extract, shown a maximum reticulocyte response and all the other expected features of a complete remission.

Minot's technique for estimating an early response to treatment by means of a reticulocyte count was a neat and most effective clinical method for control. It was probably crucial in the discovery of liver, since the occurrence of a reticulocyte crisis encouraged persistence and indicated dosage. It has since found numerous applications in clinical haematology, as well as in the elucidation of the pathology of blood disease and the evaluation of methods of treatment.

Castle's Hypothesis

The remarkable investigations of William B. Castle and his colleagues, which began in 1929 and continue even to this day, have clearly shown the role of the stomach in the production of Addisonian anaemia. The experiments,

brilliantly planned and faultlessly executed, showed the relationship between normal haemopoiesis, the diet, gastric secretion, and liver function.

Castle's work can be accounted among the greatest advances in the study of disease processes. It called attention to the vital point in Addisonian anaemia—that certain stomach secretions were essential for fundamental nutrition. The weak antiseptic action of the normal stomach juices in preventing the implantation of a haemolytic organism in the intestine, the basis of twenty-five years of treatment for Addisonian anaemia, ceased to be important almost overnight.

Castle's experimental work led him to propose (Castle *et al.*, 1930) his hypothesis that normal erythropoiesis depended upon a substance of unknown composition generally referred to as the haemopoietic or anti-pernicious anaemia principle. This principle, he suggested, was formed in the normal stomach or in the small intestine by the interaction of two factors—an extrinsic factor present in certain protein constituents of food, and an intrinsic factor secreted by the epithelial cells of the fundus of the stomach.

The haemopoietic principle, absorbed from the alimentary tract, was stored in the liver, whence it ultimately reached the bone marrow by way of the blood stream. Castle's hypothesis explained Addisonian anaemia by an absence of intrinsic factor; it had also the merit of supplying a rational explanation for most megaloblastic anaemias either by other deficiencies or by failure in the processes of absorption, transport, or storage of the haemopoietic principle.

The treatment of Addisonian anaemia quickly evolved from Minot and Murphy's great announcement, largely as the result of the work of Edwin J. Cohn and his associates, who in 1928 introduced a refined and highly potent liver extract for parenteral injection which was subsequently improved through the following decade. Somewhat later, Sharp (1929), Sturgis and Isaacs (1929), and Wilkinson (1930) showed that hog's stomach contained a substance active in the treatment of Addisonian anaemia. This factor, at first thought to be the same as that present in liver, was found to have different properties; it can now, in the terminology of Castle's hypothesis, be regarded as intrinsic factor, and can, in fact, be used to effect absorption of vitamin B_{12} from the stomach.

With increasing knowledge, however, it became clear that Castle's hypothesis was not a complete explanation, since it did not always fit new facts as they were discovered. It was, for example, found that a number of megaloblastic anaemias would respond to crude liver extracts, but not to refined and concentrated products, and this suggested that liver contained more than one substance, each or all of which might be necessary for supplying the deficiency in different types of megaloblastic anaemia.

Folic Acid and Vitamin B_{12}

This belief was eventually confirmed by the synthesis of folic acid in 1945 by Angier and his team, and the isolation of vitamin B_{12}, almost simultaneously, in 1948, by Lester Smith in England and Rickes and his colleagues in America. Studies with these substances have shown that the anti-anaemic properties of liver itself, as well as the crude extracts or products, can be attributed to both folic acid and vitamin B_{12}, whereas the refined liver extracts owe their activity to vitamin B_{12} alone. Addisonian anaemia, including the neurological complications, is now known to be due essentially to a deficiency of vitamin B_{12}, whereas most if not all of the other megaloblastic anaemias of similar haematological type are due to a deficiency of both folic acid and vitamin B_{12}, or, in some cases, of folic acid alone.

So far as Addisonian anaemia is concerned, the limitations of folic acid are now fully appreciated. Notwithstanding haemopoietic activity, folic acid fails to prevent or cure the nervous lesions associated with the disease. Indeed, excessive administration would seem to precipitate neurological complications in advanced and untreated cases of the disease by rapidly immobilizing any traces of vitamin B_{12} in the tissues, thereby creating an acute and sudden shortage of essential neurotrophic material.

Vitamin B_{12}, or cyanocobalamin, the unique cobalt-containing material which was isolated by modern methods of chemical separation, was originally prepared by an expensive process from ox-liver. It is now obtained from the metabolism fluids of a number of bacteria.

In Addisonian anaemia it is active in a daily dose as low as 1 μg., whilst a satisfactory haematological response can be obtained with as little as 20 μg. a day, and a maintenance dose of some 45 μg. every six weeks. It is also protective against the neurotrophic complications in the same somewhat uncertain and unpredictable manner as occurs with liver extracts. Experience has shown that a dosage higher than the minimum should always be used, and especially in arteriosclerotic subjects or those in whom an infection supervenes. Something of the order of 100 μg. a day is advisable until remission is complete, with a maintenance dose of 50 μg. every two weeks. Maintenance by means of massive doses at long intervals is unsatisfactory.

It is now also appreciated that most cases of Addisonian anaemia require to take iron in order to complete recovery, whilst a number may be thyroid-deficient.

Some Difficulties in Treatment

The evolution of liver treatment for Addisonian anaemia from 1926 to the present day has emphasized certain therapeutic principles, has revealed a number of complications or difficulties, and, above all, has brought to light something of the nature and mode of interaction of various related substances in the processes of haemopoiesis, especially with regard to the synthesis of substances which are fundamental constituents of a biological cell—namely, nucleic acid and its derivatives.

None would now question that Addisonian anaemia, a deficiency disease due to failure of stomach function, is incurable, and that adequate treatment must be maintained for life if haematological relapse and, above all, neurotrophic complications are to be avoided. A critical analysis (Wilkinson, 1932) of such cases as have been reported to have re-established the essential gastric function has shown quite clearly that most, if not all, are likely to have been sprue or some other alimentary disease, rather than Addisonian anaemia. Fully restored cases usually relapse in two to ten months if treatment is omitted, but some have remained well for nearly two and a half years.

Proper maintenance, with haematological control, is, however, a prime requirement, since it is really no kindness to cure a patient of Addisonian anaemia if he is afterwards to develop, and die from, preventable spinal paralysis.

Clinical experience has shown that the dosage of vitamin B_{12}, whether as such or as liver extract, should be increased in the aged, or the arteriosclerotic, and in such as develop an infective process; while septic foci should be removed. Other deficiencies may also complicate the picture, so that some with Addisonian anaemia may be found to need regular courses of iron or thyroid extract, and sometimes vitamin C, while those with neurotrophic disturbances are the better for large doses of the complete vitamin B complex, which, with calcium pantothenate, may be very effective in relieving other deficiency symptoms, such as glossitis.

In brief, the treatment of Addisonian anaemia has evolved to the point where specific curative treatment is available, with which the physician can ensure that no patient who is co-operative need die of the disease *per se*. But this is not to say that the treatment has reached a mechanical stage where neither skill nor art is required. Optimum dosage differs from patient to patient. Constant haematological and clinical supervision are necessary. Minor difficulties, such as sensitivity to liver extract, may be troublesome, and

the possibility of other incidental deficiencies should always be borne in mind, since their treatment can greatly increase the comfort and well-being of the patient.

Pathology and Biochemistry of Erythropoiesis

So much for the evolution of treatment. This survey would not, however, be complete without some short and simple account of the revelations arising from this evolution in respect of the fundamental pathology and biochemistry of erythropoiesis.

Knowledge has come from many sources, but above all from the clinical field (which would have pleased Addison), since no satisfactory technique for assay and evaluation in an animal has ever been devised. Castle, for example, had to carry out the whole of his classical work on the human subject, and likewise with the primary testing of various extracts of liver, as well as folic acid and vitamin B_{12}.

Throughout the years the hypothesis of Castle has provided an invaluable working basis for the clinician in all cases of megaloblastic anaemia. It has to be admitted, however, that the hypothesis is no longer acceptable in its original form, even though in the clinical field it still has most valuable applications, and has also provided a focusing point for new discoveries which might otherwise have become inextricably confused.

But vitamin B_{12}, which, at the outset, was thought to be the haemopoietic principle, has the natural distribution and all the properties of extrinsic factor. It cannot be absorbed in active form without gastric intrinsic factor, but, once absorbed, it behaves like the haemopoietic principle. Evidence has now accumulated to show that vitamin B_{12} itself is microbiologically active, but not haemopoietically so unless it becomes bound to intrinsic factor, possibly a mucoprotein, in the gastric juice or its counterpart in the tissues. The bond is heat-labile, and when dissociated by heat the vitamin B_{12} is no longer haemopoietically active. In Addisonian anaemia vitamin B_{12} is highly active by parenteral injection by reason of a tissue-binding substance, since it appears in the serum in bound form, but it is only active by mouth when given in massive dose (3 mg.) or in association with normal gastric juice (Ungley, 1949).

Knowledge concerning erythropoiesis has also come from studies in bacterial metabolism and animal nutrition, and, indeed, the fact that intestinal bacteria may immobilize such substances as vitamin B_{12} has an influence on therapeutics, which may be profoundly altered by a change of flora brought about by an antibiotic. Thus, the binding of vitamin B_{12} so that it is no longer available to bacteria may, in fact, be one of the essential functions of Castle's intrinsic factor, irrespective of conversion of vitamin B_{12} to a haemopoietically active form.

Functional Relationship between Folic Acid and Vitamin B_{12}

A problem of fundamental importance is a determination of the functional relationship between folic acid and vitamin B_{12}, particularly whether they are independent haemopoietic agents or whether their actions are interrelated so that the presence of one is necessary for the functioning of the other. Folic acid was at one time thought to correspond to Castle's extrinsic factor, but this obviously is not the case; and, indeed, it is difficult to fit folic acid into Castle's hypothesis at all.

The activity of folic acid seems to be dependent upon its conversion to folinic acid, otherwise known as the citrovorum factor, and so called because it is an essential growth factor for *Leuconostoc citrovorum*. Folinic acid has been shown to be therapeutically active in certain megaloblastic anaemias (Davidson and Girdwood, 1951), but, unfortunately, attempts to throw light on the relationship of folic acid, folinic acid, and vitamin B_{12} by *in vivo* and *in vitro* studies of bone marrow have produced confusing and inexplicable results. When vitamin B_{12} is injected into the bone marrow of a case of Addisonian anaemia in relapse the material is utilized by the cells, but this is not the case with either folic acid or folinic acid. On the other hand, when the materials are tested *in vitro* with megaloblastic marrow cultures, folic acid can bring about normal maturation, whereas vitamin B_{12} will not do so unless associated with normal gastric juice.

Studies of the metabolic requirements of bacteria have also shown that the pyrimidine base, thymine, can replace folic acid, and that the desoxyriboside of thymine, thymidine, can replace vitamin B_{12} in satisfying certain essential growth requirements of organisms. Both of these substances, as well as a number of others (Welch and Heinle, 1951), possess some haemopoietic activity in megaloblastic anaemias.

This rapidly accumulating tangle of facts has not as yet been unravelled, but from the angle of basic biochemistry the views of Vilter and his colleagues (1950) offer a logical and rational approach to the problem, particularly in the co-ordination of bacteriological metabolic experiments with therapeutic results in the megaloblastic anaemias.

In brief, it is suggested that all the substances which I have considered are concerned in the formation of nucleic acid, which is essential for haemopoiesis. The synthesis of nucleic acid is thought to be brought about by a "chain reaction" in which, in the first stage, folic acid, probably first converted to folinic acid, exercises a coenzyme function in the formation, from uracil and other simple substances, of purines and pyrimidines (such as thymine). In the second stage, vitamin B_{12} is thought to act as the coenzyme for the conversion of pyrimidines to nucleosides (such as thymidine) which are available for the formation of nucleotides, and so of nucleic acid. On this theory a deficiency in either folic acid or vitamin B_{12} may cause a breakdown in nucleic acid metabolism.

These views point to there being some interplay between folic acid and vitamin B_{12} in certain metabolic processes, and it may well be that the riddle of the interchangeable haemopoietic roles of these substances in Addisonian anaemia will be solved only through detailed studies of biochemical reactions.

We know that we have not yet solved all the therapeutic problems of Addisonian anaemia, much less drawn all the dividends from the discoveries which have been made since Addison first lighted a beacon a century ago. At that time he could hardly have been aware of the magnitude of the vista which he was about to illuminate, even as we do not know what will happen in the next century.

Conclusion

In a brief hour I have tried to look over the past, including the near-past in which the tempo of advance has so rapidly increased. In so doing, one remembers with gratitude the heritage of this great hospital through its many sons whom Addison inspired, most of whose contributions in the field of my subject can be found in succeeding volumes of the *Guy's Hospital Reports*.

I think of Wilks, Pye-Smith, Taylor, French, Campbell, Hurst, John Conybeare, Izod Bennett, whose pupil I once was because he came to us at Middlesex, and John Ryle, who was my immediate predecessor at Cambridge.

"Let us now praise famous men."

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ARTERIAL REPLACEMENT BY "ORLON" CLOTH*

A PRELIMINARY REPORT OF ITS EXPERIMENTAL AND CLINICAL USE

BY

J. B. KINMONTH, M.S., F.R.C.S.
Surgical Professorial Unit, St. Thomas's Hospital

G. W. TAYLOR, M.B., F.R.C.S.

AND

R. H. LEE
Surgical Professorial Unit, St. Bartholomew's Hospital

During the years since the second world war it has gradually become clear that the grafts used as substitutes for arteries served chiefly as scaffolding on which the tissues of the host developed a new vessel. The survival of cells from the donor has not proved essential for success. Indeed, good results may be obtained where no effort is made to maintain the viability of the cells of the graft. K. Nakayama (1953, personal communication) has used human homografts preserved in alcohol to replace the aortic bifurcation. In our own hands the results with heterografts sterilized and preserved in neutral formalin and used in animals have been most satisfactory over considerable periods of time. It therefore seemed a logical consequence that artificial materials might be used as a scaffold, and Voorhees and his colleagues (1952) reported the successful use of an inert plastic cloth, "vinyon-N."

Experimental Studies

Vinyon-N was difficult to obtain in England, and so we chose for trial "orlon," a plastic developed by duPont and available in Great Britain from Zurrer Silks (Darwen) Ltd., Anchor Mills, Darwen, Lancs. It was one of a variety of woven plastic materials which were easily available and likely to be chemically inert in the body. The choice was made chiefly on the naked-eye appearance of the weave and its power to hold sutures. Its ability to prevent excessive leakage of water or blood through its pores was also tested on the laboratory bench before it was used surgically. It was found to be more suitable in these ways than other materials that were tried.

Orlon is an acrylic resin, a polymer of acrylonitrile, and possesses the qualities of strong resistance to acids, alkalis, salts, and greases. The fabric used was 175 on the weft and 260 on the warp. It was inelastic, soft, and pliable, and sewed easily without tearing.

FIG. 1.—Orlon replacing portion of abdominal aorta of dog. Carrel suture used (see text).

Mongrel or greyhound dogs were anaesthetized with intravenous pentobarbitone sodium, and under aseptic conditions the peritoneum was opened through a long midline incision. The posterior peritoneum was incised, exposing the distal abdominal aorta, the lumbar arteries were ligated, and 2 to 3 cm. of aorta was resected after Blalock clamps had been applied to it above and below. The tube of orlon fabric was then sutured end-to-end to the aorta with over-and-over continuous stitches of 5/0 silk moistened with liquid paraffin, and the clamps were temporarily removed to allow blood to fill the tube and test for leaks at the anastomoses. Blood oozed through the orlon fabric for about a minute while clotting was occurring in the interstices of the fabric.

FIG. 2.—Aortogram two months after insertion of orlon. Carrel suturing not used. The upper anastomosis (arrow) is barely discernible, the lower is located by the small notch.

Animal Studies with Orlon

Dog No.	Type of Anastomosis	Result	Time (Weeks) and Method of Check	Total Time Followed (Weeks)
G.2	End-to-end	Patent	12 Necropsy	12
G.3	,,	Ruptured anastomosis	16 ,,	16
G.4	,,	Patent	21 Aortogram	21*
G.6	,,	,,	3 ,, / 15 Clinical	15*
G.7	,,	,,	8 Aortogram / 16 Clinical	16*
G.9	End-to-side	,,	4 Aortogram / 8 Necropsy	8
G.10	End-to-end	,,	10 hrs. ,,	—
G.11	Side-to-side†	Thrombosis	3 Aortogram / 5 Necropsy	5
G.12	,,	Patent	4 Clinical	4*

* Indicates animal still surviving for further study.
† All prostheses were inserted in the aorta except in G.11 (aorta to external iliac).

*Based on a communication to the Surgical Research Society, London, November 26, 1954.

FIG. 3.—Interior of orlon tube inserted end-to-side two months previously. The interior of the host aorta is visible at either end, and that of the orlon, covered by transparent new "intima," in the centre.

FIG. 4.—Microscopical section (×55) of orlon and collagen four months after insertion. Spaces near the orlon are artefacts. The thickness of collagen is greater on the exterior (see text).

When the oozing through the fabric had stopped the clamps were removed and blood was allowed to flow through the orlon tube (Fig. 1).

In some experiments (G.9, G.11, and G.12 in the Table) a shunt made of orlon was used to conduct the blood around an artificial aortic block produced by tying the aorta. The tubes of orlon were anastomosed end-to-side or side-to-side to the aorta, in which an oval window had been cut to make the aortic stoma larger. These end-to-side and side-to-side anastomoses were tried because they made possible a larger stoma than would end-to-end anastomosis, in which the stoma would, of course, be limited to a diameter equal to that of the host artery. A large stoma, and particularly one in which the suture line did not completely encircle the host vessel, should be less liable to closure by thrombosis. The end-to-side and side-to-side anastomoses worked well in the aortas of dogs in which they were tried.

The posterior peritoneum was closed over the prosthesis and the abdomen closed in layers. Penicillin and "plasmosan" were given post-operatively. At a later date patency of the grafts was determined by an aortogram performed by injecting diodone into the aorta above the prosthesis through a cardiac catheter which had been passed down into the aorta from the common carotid artery (Fig. 2).

The results in the dogs which had orlon prostheses are shown in the Table. The prostheses were implanted in their abdominal aortas or as shunts around an aortic or iliac obstruction. One (G.10) died 10 hours after operation without recovering from the anaesthetic. The prosthesis was patent and lined internally by smooth fibrin. The anastomosis was intact. Another (G.3) died at 16 weeks post-operatively from rupture of a false aneurysm that was surrounding the prosthesis and which had formed from an anastomotic leak. The orlon tube was floating in the centre of the false aneurysmal sac and had no fibrous reaction within or around it. The significance of this lack of reaction is discussed below. The suture material was found to have pulled out of the aorta at the distal anastomosis. In one animal (G.11) a 5-in. (12.5-cm.) long shunt had been placed from the aorta to the left common iliac artery, bridging a tape ligature on the iliac artery. The shunt thrombosed in the early post-operative period, and on sacrifice at four weeks the graft was found to be thrombosed and one of the distal anastomotic sutures had constricted the iliac artery. All the other orlon prostheses have remained patent. The two failures were due to technical errors which were in no way peculiar to the material or the method.

The tubes become lined with a smooth glistening layer of hyaline collagenous tissue, the innermost layer indistinguishable from intima (Figs. 3 and 4). They are surrounded by a thick layer of fibrous tissue which encases and grows into the meshes of the cloth (Fig. 5). They are tolerated without ill effect. The collagen lining and surrounding the tube results from the vascularity and activity of the surrounding tissues. This was well shown in dog G.3. Rupture of the distal suture line occurred soon after operation, and blood continued to flow through and around the tube and into the false aneurysmal sac, in which it lay almost free for several months before death. Despite this, the orlon tube looked almost as fresh as when it was inserted. There was a little fibrin deposited on it, but no collagen formation whatever. This suggests that contact with surrounding living tissues may be necessary for the collagen to form. Mere contact with circulating blood is insufficient.

Another interesting point that emerged at necropsy was the way in which the orlon retained its strength. After several months in the tissues the tensile strength of the fabric appeared to be quite unchanged. This is of great practical importance, because mere unsupported collagen would be expected to stretch under pressure and with the passage of time.

None of the prostheses and their surrounding tissues have shown evidence of calcification on *x*-ray examination.

Clinical Application

Encouraged by these results, we placed orlon tubes in three patients. Brief case summaries are presented.

Case 1

A 58-year-old male Civil Servant was admitted to St. Bartholomew's Hospital complaining of epigastric pain of three months' duration. For four years he had had intermittent claudication of the left calf, which appeared after 150 yards. For the past 18 months he had noticed increasing epigastric discomfort, which for three months had been severe and was associated with nausea, morning vomiting, and weight loss. Two months before admission he noted the appearance of a tender mass in the left mid-abdomen that had more recently increased in size.

On examination he was noted to be a thin ill-looking man who appeared older than his age. The blood pressure was 210/108. The veins in the neck were distended; the heart was enlarged and there was an apical systolic murmur. In the abdomen there was a visible swelling in the left upper portion which had an expansile pulsation, measured 5 by 12 cm., extended from the left of the umbilicus to just

FIG. 5.—Exterior of aorta and collagen-surrounded orlon removed from an animal three months after operation.

below the costal margin, and was compressible, tender, movable from side to side, but not superiorly and inferiorly. Peripheral pulses were decreased bilaterally and neither posterior tibial pulse was palpable.

Aortography showed a large aneurysm of the abdominal aorta extending from just below the kidneys down to and involving both common iliac arteries. It was evident that the aneurysm was expanding, that rupture was imminent, and that intervention was necessary. Operation was performed through a long midline incision. The aneurysm extending from 1 cm. below the kidneys to 2 cm. below the bifurcation was excised and an orlon prosthesis anastomosed end-to-end to the aorta above and to each common iliac artery below. After operation the femoral pulses were good. He experienced a fall in blood pressure during the first 30 minutes of the operation and afterwards passed little urine. His blood urea rose to 332 mg. per 100 ml. by the fourth day, and he became comatose and died. Necropsy revealed marked renal fibrosis and atheroma of the renal arteries. The orlon prosthesis was patent and the anastomosis intact. Death was due to failure of the diseased kidneys to function following the period of hypotension during operation.

Case 2

A 62-year-old male clerk of works was admitted to St. Bartholomew's Hospital complaining of pain in the leg on walking. Two years previously he had noticed that pain developed in the left calf after walking about 200 yards.

FIG. 6.—Orlon prosthesis in place on iliac vessels of Case 2 after completion of side-to-side anastomoses.

It had steadily increased in severity until the present, when it occurred after 75 yards of slow walking. He had been forced to stop work because of the pain. There was no rest pain or ulceration.

On examination the blood pressure was 200/100. Major abnormal findings were limited to the extremities, where the left foot was colder than the right, and paled quickly on elevation to 20 degrees. Pulses were completely absent on the left, but present though diminished on the right. Aortography revealed obstruction of the left external iliac artery.

The ischaemia was considered to be too severe for relief by ganglionectomy alone, and it was decided to use an arterial prosthesis. Operation was performed through a left paramedian incision. The left iliac vessels were exposed and a tube of orlon 5 in. (12.5 cm.) long was anastomosed to the left common iliac artery above the block and to the left common femoral artery below it (Fig. 6). The anastomoses were done side-to-side to make larger stomata. The existing collateral circulation was not disturbed. A left lumbar ganglionectomy was also performed. Post-operatively the pulses were all present in the left leg and stronger than in the right. Six months after operation he was able to walk three-quarters of a mile without claudication and the pulses remained present and strong.

Case 3

A 67-year-old company director was admitted to St. Bartholomew's Hospital complaining of a large pulsating swelling in the left groin. For many years he had noticed a small lump in the left lower abdomen, which three weeks before admission had suddenly enlarged and started to pulsate and had become very prominent. There was a history of three myocardial infarctions at ages 64, 65, and 66, and moderate exertional dyspnoea and angina since the last infarction.

On examination the pulse was 88 and grossly irregular; the blood pressure was 180/105. The heart was not enlarged, but auricular fibrillation was present. In the abdomen there was a large pulsating visible mass in the left lower quadrant just below the umbilicus and extending down to the inguinal ligament. Its most prominent part was pushing out the anterior abdominal wall. The pulses were diminished bilaterally and absent distal to the popliteal artery on the left. Because of its possible harmful effect on renal function, aortography was not done. Operation was performed through a long left paramedian incision and a huge abdominal aneurysm was excised. It was 8 in. (20 cm.) in antero-posterior and 5 in. (12.5 cm.) in lateral extent. A λ-shaped orlon graft was placed from 2 in. (5 cm.) below the renal arteries to 3 in. (7.5 cm.) beyond the bifurcation and anastomosed end-to-end to the aorta above and to the common iliac below. Post-operatively he has had good pulses in both legs, and the prosthesis has functioned perfectly in the five months since operation.

Preparing the Prostheses

1. *The Seam.*—Ordinary fine white nylon sewing thread (No. 102) has been used to sew the seam, as orlon thread was not available to begin with. More recently pure orlon thread has been used. No difference has been discernible in the results from the two materials. A sewing machine is used to sew the seam and three rows of stitches are inserted close together and about 5 mm. from the free edges of the cloth. The ways in which the cloth is folded and sewn can be seen in Fig. 7. Prostheses for end-to-end or side-to-side anastomosis need only one longitudinal seam, for they are made from a single piece of cloth folded upon itself. The ends of the prosthesis intended for side-to-side use are closed by seams which lie close to the stomata. This avoids having a blind bag at each end (Fig. 7). Two pieces of cloth of the same shape are placed one on the other and sewn together when a branching prosthesis is needed. More seams are then required. A prosthesis for the aortic bifurcation is shown in Fig. 7. The same principle may be used for a greater number of branches.

2. *The Ends.*—Sutures placed close to the edge of a single thickness of cloth may pull out; therefore the ends are folded over. The folding is done before sewing the seams to avoid narrowing the ends of the tube.

3. *Size.*—Rough dimensions may be obtained from angiograms. The length is estimated without great difficulty. The diameter measured from the arteriogram tends to be smaller in obliterative disease and larger in aneurysmal disease than is needed in the operation. The diameter of the prosthesis as it lies flat and undistended needs to be

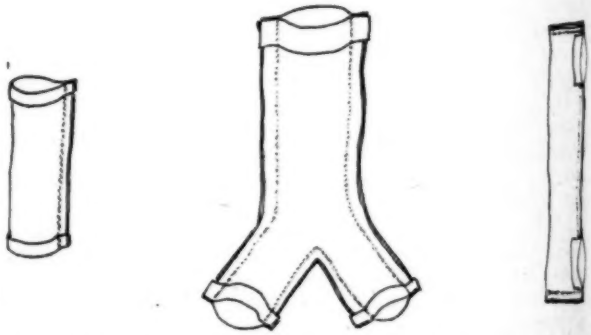

FIG. 7.—Diagrams to show folds and seams of prostheses for (from left to right) end-to-end, bifurcation, and side-to-side insertion.

approximately twice the diameter measured on the arteriogram film. It is convenient to have two or three prostheses of slightly different dimensions prepared before operation. One of them is usually found to be of the correct size. Should it prove too long it is easy to unpick some of the seam and trim it to the required length.

4. *Sterilization.*—The completed tubes are sterilized by boiling or autoclaving before operation. The latter is preferable. It is important to avoid folds or wrinkles in the cloth. The completed prostheses are smoothed with an electric iron before autoclaving. This is particularly helpful in keeping the folds at the stomata turned conveniently backwards so that suturing is facilitated when the time comes. Glass rods or small test-tubes are inserted inside the prostheses to prevent wrinkling during autoclaving.

Discussion

The advantages of these cloth prostheses over homografts are obvious. They are far more easily obtained and there is no anxiety about their sterility. They have, however, limitations. They cannot be used across the line of flexion of a joint, or certainly not if the joint is to be acutely flexed in the immediate post-operative period, for if this is done the tube is folded, the lumen obstructed, and thrombosis follows. This was the result when a prosthesis was inserted in a dog from the aorta to the femoral artery and the hip-joint flexed. Perhaps if flexion was avoided by splintage or other means until a firm collagenous wall had formed success might be obtained. Until this point is elucidated further we have avoided using a prosthesis below or across the inguinal ligament in patients, relying still upon homografts for this region.

A point of technical interest became evident when the aortograms were examined. When the classical Carrel everting suture was used a definite constriction was always produced at the anastomosis. This did not occur when a simple over-and-over running suture was used without eversion of the inner surfaces. The latter type of suture also has the advantage of greater speed and ease of execution.

The idea of using seamless tubes soon comes to mind when considering prostheses, and through the kindness of Messrs. Ethicon Sutures we have had some of these for preliminary trial. Certain disadvantages came to light which were not at first obvious. A turnover at the ends is desirable, and this necessarily produces some constriction, which is undesirable in the smaller-lumen tubes. Also, where branches are involved they are less adaptable for use compared with the prostheses made to measure. However, there is no doubt that with further trial still better prostheses will be evolved.

Summary

Experimental studies using "orlon" cloth prostheses to replace arteries of dogs are described.

The prostheses can be inserted end-to-end, end-to-side, or side-to-side into the arterial tree of the host. Branching prostheses may also be used.

Their clinical use in the treatment of arterial disease is reported.

Technical points in preparing the prostheses are outlined.

Advantages and disadvantages of prostheses compared with homografts are discussed.

We are grateful to many colleagues who have helped with this work. Professor Sir James Paterson Ross has given advice and encouragement, and Professor E. C. Amoroso has given us hospitality and facilities at the Royal Veterinary College for the animal studies. Dr. Hugh Cleland has helped with some of the operations. Miss D. Aitken has given skilled technical help, particularly in preparing the prostheses.

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SENSITIVITY TO FIVE ANTIBIOTICS OF A FURTHER 200 STRAINS OF STAPH. PYOGENES ISOLATED FROM OUT-PATIENTS

BY

E. G. REES, M.B., M.R.C.P.

R. A. SHOOTER, M.D.

(From the Department of Bacteriology, St. Bartholomew's Hospital)

AND

G. D. H. SHAWE, M.B., B.S.

Surgical Registrar in Charge of the Casualty Department, St. Bartholomew's Hospital

Three years ago a report was made from this laboratory of the sensitivity to five antibiotics of strains of *Staphylococcus pyogenes* isolated from out-patients (Birnstingl, Shooter, and Hunt, 1952). It was found that, although the majority of staphylococci isolated from in-patients at that time were resistant to penicillin, resistant staphylococci were isolated from only 32 of 200 out-patient infections. No strains were resistant to streptomycin, chlortetracycline, oxytetracycline, or to chloramphenicol. In view of the continued prevalence of penicillin-resistant staphylococci in hospital wards, and the increasing number of strains found to be resistant to the later antibiotics, we have again examined 200 strains of *Staph. pyogenes* isolated from out-patient infections to see if resistant staphylococci are responsible for more of these infections than was the case three years ago.

Sources of Staphylococci

Swabs were taken from patients with acute infections of the skin and subcutaneous tissues attending the casualty department between October, 1954, and March, 1955. Whenever possible, swabs were taken on the first attendance, or, if this was not possible, when a lesion was opened. Swabs taken from patients attending other out-patient departments of this hospital, such as the skin and ear-nose-and-throat departments, were not included in the series, and care was also taken to exclude patients attending other hospitals, or who had recently been discharged from hospital wards.

Methods of Isolation and of Testing Sensitivity

All the swabs were sown direct on to two horse-blood-agar plates from which cups had been cut with a cork-borer. After inoculation these cups were filled with penicillin 10 units/ml., streptomycin 250 μg./ml., oxytetracycline 50 μg./ml., chloramphenicol 250 μg./ml., and erythromycin 100 μg./ml. respectively. Staphylococci which coagulated plasma in a tube were regarded as *Staph. pyogenes*: those which were inhibited by antibiotics to approximately the same degree as the Oxford H staphylococcus were described as sensitive.

Dilution sensitivity tests were carried out for all the antibiotics used with the exception of penicillin. For these tests stock solutions of streptomycin calcium chloride complex (1,000 μg./ml.), oxytetracycline (100 μg./ml.), chloramphenicol (1,000 μg./ml.), and erythromycin (100 μg./ml.) were prepared in distilled water and stored at −8° C. The solutions of streptomycin and chloramphenicol were replaced every two months; solutions of oxytetracycline and erythromycin were made up weekly. For testing, series of two-fold dilutions of each of the four antibiotics in nutrient agar plates were prepared immediately before use, each plate

containing 14 ml. of nutrient agar and 1 ml. of a solution of antibiotic of such strength as to give the required concentration when uniformly diffused in the medium. Each plate was divided by diamond marking into 12 approximately equal sectors of just over 5 square cm. An 18-hour nutrient broth culture of each staphylococcus was used as the inoculum, a 1-mm. loopful of the undiluted culture being spread over each sector. (For streptomycin, tests were also made using this inoculum diluted 300 times.) The plates were incubated at 37° C. for 18 hours, and the end-point was determined by inspection of the surface of the medium.

Results

For *Staph. pyogenes*, resistance to penicillin is dependent on the production of penicillinase, and as this can be detected in primary culture no further examination was thought necessary. Of the 200 strains isolated, 43 produced penicillinase and were resistant. Sensitivity to the other antibiotics is shown in the Table. With one exception strains found sensitive by the dilution method had already been so described on primary isolation.

Sensitivity of 200 Strains of Staph. pyogenes to Streptomycin, Oxytetracycline, Chloramphenicol, and Erythromycin

Minimum Inhibitory Concentration (μg. per ml.)	Streptomycin		Oxytetracycline	Chloramphenicol	Erythromycin
	Undiluted Inoculum	1 in 300 Inoculum			
>64	1	—	—	—	—
64	1	—	—	1	—
32	26	—	—	1	—
16	87	—	—	186	—
8	67	1	—	12	—
4	17	4	—	—	—
2	1	103	38	—	—
1	—	90	119	—	13
0·5	—	2	42	—	187
0·25	—	—	1	—	—

We have deliberately used a heavy inoculum when testing sensitivity, partly to enable a comparison to be made with previous work, and partly in the belief that the results obtained may be more applicable to conditions in the body (Spink, 1951). In a small pilot experiment involving 12 strains it was found that for oxytetracycline, chloramphenicol, and erythromycin, the difference between an inoculum of undiluted culture or a 1 in 300 dilution of undiluted culture amounted to only one serial dilution of the antibiotic. For streptomycin the difference was greater, and the results are accordingly reported as those obtained with undiluted culture or its 1 in 300 dilution.

Discussion

Penicillin.—In the three years since the last survey much penicillin has been prescribed in general practice, and many members of the public have entered and left hospital wards. A considerable number of this last group of patients must have taken with them to the outer world penicillin-resistant hospital staphylococci, and it is gratifying and perhaps a little surprising that we have isolated only 43 resistant strains (21.5%), as compared with 16% three years ago. The spread of resistant staphylococci within hospitals has been so rapid that it might be thought that there is some special feature of the hospital environment which encourages them in preference to sensitive strains. Perhaps in the outer world sensitive staphylococci are better able to hold their own, and a 21.5% rate represents a state of equilibrium.

Streptomycin.—With the use of a heavy inoculum two of our strains were relatively resistant to streptomycin, but that this represents the selection of a few resistant variants is suggested by the finding that all the strains were sensitive when tested with a dilute inoculum. There are few indications for the use of streptomycin in the treatment of staphylococcal infections, and it was included as a matter of theoretical interest.

Other Antibiotics.—Resistance to oxytetracycline, chloramphenicol, erythromycin (and streptomycin) is the result of exposure of staphylococci to these drugs, and resistance, once acquired, is permanent. This type of resistance is becoming an additional characteristic of hospital staphylococci, and its occurrence is related to the frequency with which the newer antibiotics are prescribed. That we have found only one staphylococcus to be resistant to chloramphenicol and none to be resistant to the other antibiotics presumably reflects the relatively restricted use of antibiotics in general practice, and the dilution among the general public of resistant hospital strains.

If *in vitro* sensitivity tests can be taken as a guide to the likely outcome of treatment—and for most infections and drugs there is general agreement that they can—our findings would suggest that some 80% of staphylococcal infections originating outside hospital will respond to treatment with penicillin, and almost all to treatment with oxytetracycline, chloramphenicol, and erythromycin.

Summary

Two hundred strains of *Staph. pyogenes* isolated from out-patients with acute staphylococcal infections of the skin and subcutaneous tissues have been tested for their sensitivity to penicillin, streptomycin, oxytetracycline, chloramphenicol, and erythromycin. Of the strains tested, 21.5% were resistant to penicillin. One strain was resistant to chloramphenicol, and none to the other antibiotics.

Comparison of these results with those of a similar investigation carried out three years ago has shown that there has been a slight increase in the proportion of strains resistant to penicillin, but virtually no increase in strains resistant to the other antibiotics.

We are indebted to Professor L. P. Garrod for advice, and to Miss M. Rhodes for technical assistance.

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TREATMENT OF THE PREMENSTRUAL SYNDROME

VALUE OF ETHISTERONE, MEPHENESIN, AND A PLACEBO COMPARED

BY

G. I. M. SWYER, D.M., D.Phil., M.R.C.P.

Consultant Endocrinologist, Department of Obstetrics, University College Hospital

In a recent penetrating contribution on the premenstrual syndrome Greene and Dalton (1953) reached the conclusion that the wide variety of distressing symptoms from which many women suffer during the final week or so of the menstrual cycle, and occasionally at other points of the cycle, are probably due to water-retention. This, in turn, they felt was very likely the result of an abnormal elevation of the oestradiol/progesterone ratio. Claims for the beneficial results of treatment aimed either at dehydration or at correcting the alleged hormonal disturbance have, they point out, been made by a number of writers. They themselves found treatment by a progestogen to be almost invariably successful, in mild cases relief usually being obtained by the oral administration of ethisterone in a dosage of 25 mg. twice daily during the second half of the menstrual cycle. Still more effective was the intramuscular injection of progesterone, 25 mg. on alternate days during

the same phase of the cycle, or the implantation of progesterone, which then remained available for many months.

My own experiences with ethisterone, used in much the same way as above, had been less convincing of its efficacy. Moreover, it has seemed probable that psychological factors, leading to the tension-pain syndrome, might constitute a not unimportant part of the premenstrual syndrome, so that the administration of a muscle-relaxing drug might be expected to have some value in the management of the condition. There have already been reports that mephenesin ("myanesin"; 3-(2-methylphenoxy)propane-1 : 2-diol) administered orally to patients with disturbed psychic functions manifested as anxiety could produce sedation without soporific effect (Schlan and Unna, 1949); and Ström-Olsen (1951) found this drug to be of value in combination with psychotherapy in relieving tension states. There seemed to be good reason, therefore, for submitting the use of mephenesin orally in the treatment of premenstrual symptoms to clinical trial, and at the same time to compare its value with that of ethisterone.

Plan of the Experiment

Since the assessment of the patients' symptoms could only be subjective, it was clearly necessary to adopt a plan which would eliminate, so far as possible, both patient and observer bias. The use of a placebo, indistinguishable from the active tablets, was a prime requirement, and ignorance of the nature of each set of tablets, both by the patient and, at least until after the result had been recorded, by the observer, was equally important. The scheme employed therefore consisted of four groups of treatments: placebo; ethisterone, 10 mg.; mephenesin, 0.5 g.; and ethisterone, 10 mg., + mephenesin, 0.5 g. All the tablets, of course, looked alike and were put up in numbered boxes, a complete set of the four treatments, in prearranged order, being contained within a larger numbered box. It was intended that each patient in the trial should have each of the four treatments in successive months, in random order, the actual order remaining unknown to the observer until the end of the trial. This therefore called for $4!$, that is 24, patients for a complete series.

The patients were women attending the Fertility and Endocrine Clinics of the Obstetric Hospital, University College Hospital, and employees of the Savings Bank division of the General Post Office (kindly referred by Dr. Mary Parkes). The nature of the trial was explained to them—namely, that they would be having four different treatments in successive months, and would be asked which seemed to be effective. A record was made of their age, parity, the duration of their premenstrual symptoms, whether the latter were mild or severe, and whether they were constant or inconstant from one cycle to another. They were entered into the trial in the order in which they presented themselves and were given the first box of tablets from the appropriate large container. They were told to take one tablet five times a day for 10 days, starting on the 15th day of the cycle, and to return a month later.

On their return the effect of treatment in the cycle just finished was scored as ++ if symptoms were completely abolished; + if there was some, but incomplete, improvement; 0 if the symptoms were unchanged; and − if the symptoms were worse, or additional symptoms, thought to have been caused by the treatment, were noticed. They were then given the second box of tablets, and so on until all four months of treatment had been accomplished. Naturally, in a trial of this kind, it is inevitable that, for one reason or another, not every patient completes the planned series of treatments.

Results

The clinical details of the patients, and their results with the individual treatments, are shown in Table I. From this it is at once clear that there is considerable variation in the severity and variability of the symptoms from patient to patient, and in the same patient from cycle to cycle. This naturally makes the assessment of the value of different treatments more difficult.

Table II shows the results of treatment for each successive month, regardless of the treatment actually used. It would

TABLE I.—*Details of Patients and Their Individual Results*

No.	Age	Parity	Duration of Symptoms	Symptoms		Months of Treatment 1	2	3	4
1	24	0	3 yrs.	Severe	Constant	A+	Conceived in this cycle		
1a	37	0	>10 ,,	,,	,,	A0	B+		
2	30	2	>6 ,,	Mild	,,	B0	A−	C−	D−
3	34	2	3 ,,	Severe	Variable	B+	C+	A+	D0
4	35	2	15 ,,	,,	Constant	B0	C0	D0	A0
5	33	0	>10 ,,	,,	,,	A−	D−	B0	C−
6	40	0	>5 ,,	Mild	Variable	D−	A+	B0	C−
7	31	0	3 ,,	Severe	Constant	C−	D−	A+	B+
8	31	0	>5 ,,	,,	Variable	C+	B0	D++	A++
9	37	0	>5 ,,	,,	Constant	A++	C0	D+	B+
10	41	0	>5 ,,	,,	Variable	C+	A++	D+	B−
11	18	0	4 ,,	,,	,,	B0	C+	A0	D+
12	34	1	5 ,,	,,	Constant	C0	D0	B+	A++
13	24	0	8 ,,	,,	Variable	A+	B0	D+	C++
14	21	0	>5 ,,	Mild	Constant	B++	A0	C+	D++
15	18	0	3 ,,	Severe	,,	B0			
16	30	0	3 ,,	,,	,,	B−	D+	C+	A++
17	33	0	20 ,,	,,	Variable	A++	C0	B+	D++
18	20	0	6 ,,	Mild	Constant	C+	A++	B++	Pregnant
19	34	0	20 ,,	,,	,,	D−	C++	A++	B+
20	18	0	1 ,,	Severe	,,	A+	B++	C+	D0
21	16	0	1 ,,	Mild	,,	A−	D0	C+	B+
22	37	0	10 ,,	Severe	,,	D0	A−	C++	B+
23	32	0	5 ,,	,,	Variable				
24	17	0	1 ,,	Mild	,,	D−	C+	B+	A0

A = Mephenesin. B = Ethisterone. C = Mephenesin + ethisterone. D = Placebo. ++ = Very good. + = Good. 0 = No effect. − = Side-effects.

TABLE II.—*Results of Treatment by Months Irrespective of Actual Treatment*

Month	Very Good	Good	Total	No Effect	Side-effects	Total
1	3	7	10	7	7	14
2	4	6	10	8	4	12
3	4	12	16	4	1	5
4	5	7	12	4	4	8

TABLE III.—*Comparison of Results in First and Second Months with those in Third and Fourth*

Months	Good	No Good
1+2	20	26
3+4	28	13

TABLE IV.—*Results of Treatment by Different Treatments, Irrespective of Months*

Treatment	Very Good	Good	Total	No Effects	Side-effects	Total
Mephenesin	8	6	14	5	4	9
Mephenesin + ethisterone	3	10	13	4	4	8
Ethisterone	3	10	13	8	2	10
Placebo	2	6	8	6	6	12

TABLE V.—*Comparison of Mephenesin versus the Rest*

Treatment	Good	No Good
Mephenesin + (mephenesin + ethisterone) ..	27	17
Ethisterone + placebo	21	22

TABLE VI.—*Comparison of Ethisterone versus the Rest*

Treatment	Good	No Good
Ethisterone + (ethisterone + mephenesin) ..	26	18
Mephenesin + placebo	22	21

appear that fewer good results were obtained during months 1 + 2 than during months 3 + 4; this is more apparent in Table III. The difference is not significant ($\chi^2 = 1.302$); nevertheless it seems possible that the suggestibility of the patients may have been heightened towards the latter part of the trial, so that those who had not yet experienced relief from the treatments they had had so far presumably thought that some of the later treatments ought to be effective.

Table IV sets out the results of the different treatments, irrespective of months. It will be seen that complete relief of symptoms occurred most often with mephenesin, but that when the "very good" and "good" results combined were compared with the poor results, there was not much to choose between mephenesin, ethisterone, or mephenesin + ethisterone. The placebo, though less effective than the above, was by no means devoid of apparent value.

Tables V and VI compare mephenesin with the rest and ethisterone with the rest. The similarity in these groups of figures will be noticed. None of these differences is statistically significant.

Discussion

The results of this limited trial suggest that both ethisterone and mephenesin have some value in the treatment of the premenstrual syndrome, but that neither can be expected to help more than about 60% of patients. The combination of mephenesin and ethisterone appears to be no better than either substance alone. Mephenesin alone completely relieved eight patients, whereas ethisterone and ethisterone + mephenesin had this effect on only three each, and the placebo did as well in two patients. Table I shows that of the 21 patients who had all four treatments, only 3 had no relief from any treatment, 10 benefited from either ethisterone or mephenesin, and 8 appeared to be helped by both.

The incidence of side-effects was notably low both with mephenesin and with ethisterone; in point of fact, more complaints of these were recorded for the placebo than for the other tablets.

Since in this trial either ethisterone or mephenesin alone helped some 60% of patients, and one or the other was of some value to about 90% of the patients, it is apparent that hormonal imbalance may not be the sole cause of the symptoms in at least some of the patients. The evidence suggests that psychological factors, manifesting themselves in tension states, may be an important part of the premenstrual syndrome in some cases, and where successful treatment does not follow from ethisterone therapy the use of mephenesin might well be considered.

Summary

A clinical trial of ethisterone and of mephenesin alone and in combination, for the treatment of premenstrual symptoms has been carried out by means of a random block design, whereby the effects of the various treatments could be compared with each other and with those due to a placebo.

While mephenesin produced complete relief more often than ethisterone, an overall analysis suggests that there is little to choose between them. Either substance alone helped only some 60% of patients, and a combination of the two was no more effective; but one or the other was of some value to about 90% of the patients.

My thanks are due to Dr. Mary Parkes for referring the majority of the patients to me for the purposes of this trial; and to Dr. B. M. Merriman, of British Drug Houses Ltd., for supplying the sets of tablets.

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ANTERIOR TIBIAL SYNDROME FOLLOWING ARTERIAL EMBOLISM

BY

D. C. WATSON, *M.C.*, M.D., M.R.C.P.
Senior Medical Registrar, United Liverpool Hospitals

(From the Liverpool Royal Infirmary)

Carter *et al.* (1949) described a syndrome consisting of ischaemic necrosis of the muscles of the anterior tibial compartment of the leg, with a lesion of the anterior tibial nerve. Their 10 patients were fit young men, in eight of whom the onset was clearly related to strenuous unaccustomed exercise involving the use of the leg muscles. The condition developed in their two remaining cases after transfusion into the affected limb. The main clinical features were pain, swelling, redness, and tenderness in the front of the leg. There was inability to dorsiflex the foot and toes. The peroneal muscles were not affected. Involvement of the anterior tibial nerve produced paralysis of the extensor digitorum brevis muscle and sensory loss on the dorsum of the foot. The degree of residual foot-drop was lessened by the development of contracture in the affected muscles.

Vogt (1943) described the first similar case. Sirbu *et al.* (1944) described one case in which both legs were affected after marching, and another which followed repair of a small muscle hernia through the anterior crural fascia. Horn (1945) reported two cases in young soldiers after marching, and Phalen (1948) described the case of a young man who developed the syndrome after walking half a mile. The case of a young Greek who showed the same condition in both legs after long-jumping on a concrete pavement was recorded by Pearson *et al.* (1948). Hughes (1948) described three cases of "ischaemic necrosis of the anterior tibial muscles due to fatigue." Two were in healthy men who played football before the onset of their symptoms, and the third case occurred in a young man suffering from a febrile systemic illness, possibly polyarteritis nodosa. Tillotson and Coventry (1950) described a case in a hiker following his first walk of the season. Horn and Sevitt (1951) reported a case in which the syndrome was included in the sequelae of a traumatic rupture of the popliteal artery. Similar symptoms were noted by Psaki and Schields (1952) in a soldier who sustained a twisted ankle.

Below, two cases are described in which the syndrome followed arterial embolism.

Case 1

A woman aged 51, who had chronic rheumatic heart disease, with aortic incompetence, mitral stenosis, and controlled auricular fibrillation, was admitted to hospital on May 25, 1954. There was a moderate degree of peripheral arteriosclerosis. She complained of severe pain, of sudden onset, in the right calf. The right lower limb was found to be cold and pale up to a handbreadth below the knee; the toes were deeply cyanosed, and gangrene appeared likely. The right popliteal pulsation was much weaker than the left and no pulsations could be felt at the right ankle. The right femoral pulsation and all pulses in the left lower limb were normal. A diagnosis of arterial embolism was made and treatment begun with analgesics and oral vasodilators (nicotinic acid, 100 mg., and tolazoline hydrochloride, 25 mg., both thrice daily). The affected leg was exposed and the foot supported in a right-angled splint.

On May 26 she complained of severe pain in the front of the right leg, and this region was seen to be swollen. The maximum calf circumferences were right 12 in. (30 cm.) and left 10½ in (26.5 cm.), but measurements from the fibulae posteriorly round to the anterior tibial borders were equal. The swollen area was bright red in colour, fading a little in the lower third of the leg, and very tender. The patient was unable to dorsiflex the foot and toes. Voluntary movement was present in the peroneal and posterior tibial muscle groups but was limited by pain. The right ankle-jerk, which had previously been normal, was now diminished. Sensation to light touch and to pinprick was reduced in the lower part of the leg and was absent over the toes and dorsum of the foot.

Over the next three weeks the condition of the right leg slowly improved, though pain remained troublesome. The toes became normal in appearance and the temperature of the leg and foot increased slightly. A weak right posterior tibial pulse became palpable. The redness and tenderness diminished, becoming more localized in the upper third of the leg. There was some reduction in the swelling of the anterior tibial compartment, but dorsiflexion of the foot and toes remained impossible. Sensation returned to the lower part of the right leg and foot, though not to a small area on the dorsum of the foot proximal to the first interdigital cleft.

On June 16 the patient suddenly became unconscious and died after ten minutes. It was thought that a cerebral embolus was responsible, but permission for necropsy was not obtained.

Case 2

A woman aged 70, who suffered from mild hypertension and auricullar fibrillation, was admitted to hospital on November 10, 1953. She gave a history of sudden onset of severe pain in the left calf, beginning seven hours before admission. Examination showed considerable peripheral arteriosclerosis. The left lower limb was cold and pale from the knee downwards and the popliteal and ankle pulses were absent. The left femoral pulsation and all pulses in the right lower limb were present and normal. The patient was unable to dorsiflex the foot and toes. The peroneal and posterior tibial muscles showed slight weakness. The left ankle-jerk was reduced and all forms of sensation were diminished below the left knee. A diagnosis of arterial embolism was made. Treatment consisted of analgesics, elevation of the head of the bed, and exposure of the affected limb. The foot was supported in a right-angled splint. Tolazoline hydrochloride was given orally—50 mg. thrice daily. Papaverine sulphate (60 mg.) was given by intra-arterial injection (Edwards *et al.*, 1952). Paravertebral lumbar sympathetic block was performed (Dr. G. Jackson Rees) on November 11 and 12.

On November 13 the patient complained of pain in the front of the left leg. Examination showed redness of the skin over the anterior tibial compartment with some swelling and acute tenderness. The redness gradually faded over the next three weeks, as did the tenderness. The swelling subsided in about six weeks and the anterior tibial muscles then felt woody. During this period the left leg and foot became warmer. The peronei and posterior tibial muscles regained normal power, but there was no recovery of dorsiflexion of the foot and toes. Sensation to light touch and to pinprick returned to the leg and foot.

By January 8, 1954, she was able to walk. Although passive plantar flexion of the left foot was partly limited by contracture of the anterior tibial muscles, the degree of foot-drop required a toe-raising spring. Domestic circumstances delayed her discharge from hospital until April 9. At this time the anterior tibial muscles still felt woody and showed no wasting. A weak left dorsalis pedis pulsation had become palpable, though the left foot remained colder than the right. She did not attend for follow-up, and inquiries revealed that she died at home on May 26, the cause of death being a cerebral vascular accident.

Discussion

Although these cases occurred in older patients, and although the main clinical features did not appear for two to three days after the embolism, they conform to the description of the anterior tibial syndrome. This syndrome has not previously been described following arterial embolism. Haimovici (1950) does not include it in a review of peripheral arterial embolism and its sequelae. Mufson (1952), discussing the neurological complications of peripheral vascular disease, does not mention the condition.

Two main views have been put forward to explain the production of ischaemic necrosis of the muscles of the anterior tibial compartment. The walls of the compartment do not allow of rapid distension, and Carter *et al.* (1949) suggested that a raised pressure within the compartment, produced either by the muscle trauma of unaccustomed exertion or by leakage of transfused fluid along the tendon sheaths, was the main causative factor and operated by reducing the blood supply to the affected muscles. Hughes (1948, 1949) considered that the syndrome had a primarily vascular basis and showed that the histological changes were similar to those found in Volkmann's ischaemia. He pointed out that an increased tension in the compartment should affect all muscles equally. There was in fact a varying incidence of damage to the three muscles in the anterior tibial compartment, and he suggested that this variation might be related to differences in their blood supplies. He concluded that segmental spasm of the anterior tibial artery was responsible for the syndrome.

The two present cases lend support to the view that the anterior tibial syndrome has its origin in vascular inadequacy. Profound arterial spasm is a well-recognized concomitant of embolic arterial occlusion. The appearance of the syndrome after an interval of two to three days may have been due to a delayed improvement, either spontaneously or as a result of treatment, in the blood supply to the leg muscles. This would cause swelling of the muscles, and in the anterior tibial compartment increased tension might well lead to further interference with blood supply. The cases described by Carter *et al.* (1949) following exertion or transfusion did not show any significant impairment of peripheral blood flow in the limbs affected, but the shortest interval between symptoms and examination was one week in nine of their ten cases. It seems possible that spasm of the anterior tibial artery may have occurred in these cases, passing off before the development of the syndrome. This explanation must remain hypothetical until similar cases are studied at the earliest stage.

Carter *et al.* (1949) differentiated the anterior tibial syndrome from cellulitis of the leg, osteomyelitis of the tibia, tenosynovitis, acute thrombophlebitis, and traction lesions of the lateral popliteal nerve. Ferguson and Liversedge (1954) described nine cases of ischaemic lateral popliteal nerve palsy. These cases differed in certain important respects from the anterior tibial syndrome (involvement of the peroneal group, muscle wasting, and electromyographic findings), though three cases appear to have followed acute arterial occlusion, and one developed after a transfusion and another after an injection, into the saphenous vein.

In discussing treatment of those cases of the syndrome which followed undue exertion involving the legs, Carter *et al.* (1949) advised graduated training as a prophylactic measure. For the acute stage they suggested complete rest of the affected limb, and, if improvement did not occur, surgical decompression of the anterior tibial compartment by fasciotomy. The necrotic muscles are, however, prone to infection (Hughes, 1948). Decompression was considered in the two cases now described but not employed, as it was felt that the onset of gangrene might thereby be hastened. Psaki and Schields (1952) described improvement in muscle power following lumbar sympathectomy as late as eleven months after the first symptoms. If spasm of or obstruction to the anterior tibial artery is indeed a causative factor, measures

designed to relieve vasospasm or to promote vasodilatation will be valuable, particularly at an early stage. When there is clinical evidence of raised tension in the anterior tibial compartment surgical decompression would seem to be reasonable, if by so doing survival of the limb is not prejudiced.

Summary

Two cases in which the clinical features of the anterior tibial syndrome followed arterial embolism are described. Pathogenesis, diagnosis, and treatment are briefly discussed.

I am indebted to Dr. E. T. Baker-Bates (Case 1) and to Dr. C. S. McKendrick (Case 2) for permission to report these cases.

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THE ROLE OF SULPHONAMIDES IN THE INFECTIVE DIARRHOEAS OF AFRICAN CHILDREN

BY

LORNA G. MACDOUGALL, M.B., Ch.B., D.C.H.
Medical Officer, King George VI Hospital, Nairobi

The problem of diarrhoea in infancy and childhood has been the subject of much research; owing to the multiplicity of causes a very careful clinical, bacteriological, and biochemical assessment may be required before an accurate diagnosis can be made and effective treatment selected.

In many tropical and backward countries immediate laboratory services are not always available, medical personnel is limited, and clinical examination alone may fail to reveal the presence of more than one disease. The discovery of otitis media or pneumonia in a child presenting with diarrhoea does not preclude the fact that there may be a coexisting bacillary dysentery even in the absence of blood and mucus in the stools.

The problem of selecting treatment is equally complex if one is to provide a satisfactory standard of therapy within the economic limits of a rapidly developing community.

In infantile gastro-enteritis in which no pathogenic organisms are isolated from the stools, sulphonamides are considered to be of doubtful value, and a regime of graduated feeding and parenteral fluids (with or without the more recent antibiotics) still forms the basis of treatment. In bacillary dysentery sulphonamides are widely used and the "non-absorbable" compounds have been accepted as the standard treatment in many countries.

Present Investigation

The original object of the present experiment had been to assess the efficacy of the "absorbable" sulphonamide sulphadimidine ("sulphamezathine"), as compared with the "non-absorbable" compounds, sulphaguanidine and phthalylsulphathiazole ("thalazole"), in the treatment of bacillary dysentery in children. As it proved impracticable to await the result of a stool culture before beginning treatment, it was decided that all cases presenting with diarrhoea as their main symptom should be included in the trial.

Although the scope of the trial was thus widened to include many possible diseases and the scientific limitations were fully realized, it was hoped that the results might be of some value to others in assessing the efficacy of sulphonamides in the treatment of infantile dysentery and non-dysenteric diarrhoea, and establishing, if possible, the drug of choice.

Sulphaguanidine has become well established in the treatment of bacillary dysentery and is recommended as the most suitable drug in tropical countries because there is little or no danger of crystalluria, and it has the advantage of rarely causing unfavourable side-effects (Boyd, 1951; Scadding, 1944). It is considered most effective in the early stages of an acute attack, but of least value when treatment is started late in the illness (Lyon, 1943; Brewer, 1943). This is of considerable practical importance in communities who do not seek medical advice until local remedies have failed and the disease is in an advanced or chronic stage. A further disadvantage so far as children are concerned is the high dosage of sulphaguanidine which is recommended. In an acutely ill and dehydrated child there is often difficulty in ensuring that the appropriate dose is swallowed.

Poth and Ross (1944) claim that phthalylsulphathiazole is highly specific in Flexner dysentery and have also proved it of value in the treatment of non-dysenteric diarrhoea. This, however, has not been borne out by Brodie *et al.* (1946), who found that it took longer to effect a cure with phthalylsulphathiazole than with either sulphaguanidine or controls, but that it reduced considerably the number of bacteriologically positive cases during convalescence. Both sulphaguanidine and phthalylsulphathiazole have the disadvantage of failing to control a parenteral or secondary infection which may complicate or perpetuate the state of diarrhoea.

Since it is known that the dysentery organisms inhabit the mucous membrane lining of the intestinal tract, the "absorbable" sulphonamides have the advantage of reaching the source of infection both through the lumen of the gut and via the blood stream (Hardy and Watt, 1944).

From previous experiments (Hardy, 1945) sulphadiazine has been recommended as the sulphonamide of choice in bacillary dysentery, with sulphadimidine of almost equal efficacy. Watt and Cummins (1945), however, place sulphadimidine in the undesirable class of sulphonamide owing to the greater percentage of toxic reactions observed in their series.

Although the possibility of renal complications with "absorbable" sulphonamides must always be borne in mind, particularly in hot climates, sulphadimidine is reported to be more highly soluble in all urines than sulphadiazine (M.R.C., 1945), and was therefore chosen for use in the present trial.

Realizing, therefore, the various advantages and disadvantages of the drugs employed, the experiment was designed as follows:

Selection of Cases.—All infants and children entering the medical wards of King George VI Hospital, Nairobi, with the main presenting symptom of diarrhoea, were admitted to the series and each succeeding case was treated with phthalylsulphathiazole, sulphadimidine, and sulphaguanidine respectively.

Clinical Assessment.—The severity of each case on admission was classified as follows: mild, moderate, severe, or moribund. As it was rarely possible to obtain an accurate history from the parents regarding the length of illness and the number or character of the stools passed daily, the clinical assessment was made on the general appearance, toxicity, and hydration of the patient. This assessment and the subsequent daily records of progress were made personally to ensure uniformity throughout the series. The groin temperature was recorded twice daily.

Dosage.—Although all children in the present series were weighed on admission, it was realized that this could not always be done in out-patient departments and the more isolated hospitals. The scheme of dosage was therefore assessed according to age (Table I) and appropriate adjustments were made for emaciated and undernourished children. Each dose was given in the form of a suspension and the appropriate dose administered at six-hourly intervals.

TABLE I

	Phthalylsulphathiazole and Sulphadimidine	Sulphaguanidine
Adults	4 g. daily	10 g. daily
8–12 years	3 g. ,,	8 ,, ,,
4–8 ,,	2·5 g. ,,	6 ,, ,,
2–4 ,,	2 g. ,,	4 ,, ,,
6 months–2 years	1·5 g. ,,	3 ,, ,,
0–6 months	1 g. ,,	2 ,, ,,

TABLE II

	Phthalylsulphathiazole	Sulphadimidine	Sulphaguanidine
No. of cases	107	107	103
Clinical condition on admission:			
Mild	16	26	21
Moderate	38	23	31
Severe	31	40	30
Moribund	22	18	21

A total of 317 African children were treated, with an average age of 1 year and 8 months. Table II shows the distribution of cases and the clinical condition on admission.

Results

Treatment was limited to a seven-day period, and if there was no response at the end of this time the trial drug was discontinued and other therapy instituted.

The response to treatment is shown in Table III; although the total number of cases in the sulphaguanidine series fit for discharge within the trial period was fewer than in either the phthalylsulphathiazole or the sulphadimidine series the figure is not significant.

In an assessment of the bacteriological results (Table IV) phthalylsulphathiazole appeared less effective in the cases of proved bacillary dysentery, but gave a higher percentage of negative cultures in the non-dysenteric group, whereas sulphadimidine showed a higher percentage of negative cultures in the Shigella group and less in the non-dysenteric series. The results with sulphaguanidine were similar in both groups. These figures, however, are not significant, and it can be said that the three drugs are of equal efficacy as regards both sterilization of stools and general clinical improvement.

TABLE III

	Phthalylsulphathiazole	Sulphadimidine	Sulphaguanidine
No. fit for discharge between 3rd and 6th days	24	30	17
No. fit for discharge on 7th day	49	44	46
No. still febrile on 5th, 6th, or 7th day	26	26	35
Total No. discharged within trial period	73 (68·2%)	74 (69·1%)	63 (61·1%)

TABLE IV

	Phthalylsulphathiazole	Sulphadimidine	Sulphaguanidine
Total No. with proved shigellae	50 (46·7%)	48 (44·9%)	48 (46·6%)
Shigellae present Day 1	44	41	43
Negative culture Day 5	17 (38·6%)	21 (51·2%)	20 (46·5%)
No pathogens Day 1 but shigellae isolated Day 5	6	7	5
Salmonellae, *B. proteus*, or *B. paracolon* isolated Day 1	18	22	19
Negative culture Day 5	10 (55·5%)	8 (36·4%)	9 (47·3%)
No pathogens throughout	39	37	36
Total No. deaths	15	16	13
No. showing shigellae	9	8	7

Of the Shigella organisms isolated throughout the series, 70% were *S. flexneri*, 11% *S. schmitzii*, 4% *S. sonnei*, and 15% were classified as atypical Shigella organisms. No difference was noted in the efficacy of the three trial drugs against these different strains, and the few Sonne infections encountered were no more resistant to treatment than the Flexner or Schmitzi infections or the atypical organisms.

No oliguria, anuria, or other obvious toxic reactions were encountered with any of the drugs under trial, and the number of parenteral infusions required was the same for each group.

In the sulphadimidine series it was noted that other chemotherapy was required in a significantly smaller number of cases (Table V) than with either of the "non-absorbable" compounds, despite the fact that the incidence of parenteral complications was approximately the same in all groups.

TABLE V

	Phthalylsulphathiazole	Sulphadimidine	Sulphaguanidine
No. requiring infusions	35	32	35
,, ,, other chemotherapy	33	14	29

TABLE VI

Parenteral Infections	Phthalylsulphathiazole			Sulphadimidine			Sulphaguanidine		
	No. of Cases	No. Showing *B. proteus*, *B. paracolon*, or Salmonellae	No. Showing Shigellae	No. of Cases	No. Showing *B. proteus*, *B. paracolon*, or Salmonellae	No. Showing Shigellae	No. of Cases	No. Showing *B. proteus*, *B. paracolon*, or Salmonellae	No. Showing Shigellae
Pneumonia	13	1	7	16	1	10	11	1	5
Pulmonary tuberculosis	6	—	4	6	—	2	3	—	2
Bronchitis	5	—	2	5	—	2	1	—	1
Upper respiratory tract infection	3	1	—	—	—	—	3	1	2
Otitis media	1	1	—	1	—	—	2	—	2
Thrush	3	—	1	4	—	2	2	—	—
Conjunctivitis	2	1	—	—	—	—	—	—	—
Poliomyelitis	—	—	—	2	1	1	—	—	—
Laryngitis	—	—	—	1	—	1	—	—	—
Cellulitis	—	—	—	1	—	1	—	—	—
Pyelitis	—	—	—	1	—	1	—	—	—
Malaria	—	—	—	1	—	1	—	—	—
Encephalitis	—	—	—	—	—	—	1	—	1
Nephritis	—	—	—	—	—	—	—	—	1
Total	33	4	14	38	2	21	23	2	14

Table VI gives an indication of the variety of parenteral infections encountered among children presenting with diarrhoea and shows the incidence of dual infections among the cases of proved bacillary dysentery. From these figures it has been estimated that of the 146 cases of proved bacillary dysentery throughout the entire series 33.5% had a co-existing parenteral infection.

Summary and Conclusions

In tropical countries where diarrhoea is a common presenting symptom in children, and large numbers of cases are seen by a limited number of medical personnel, the problem of making a precise diagnosis can be very difficult, particularly if hospital and laboratory facilities are not immediately available.

Under these circumstances treatment must of necessity be simple, giving the optimum facilities to the greatest number of patients, whether treatment be undertaken in out-patient dispensaries, clinics, or district hospitals.

A survey was therefore made of 317 cases of diarrhoea in African children, each succeeding case being treated with phthalylsulphathiazole, sulphadimidine, and sulphaguanidine respectively, with the aim of establishing the relative merits of the "absorbable" and "non-absorbable" sulphonamides in the treatment of bacillary dysentery and non-dysenteric diarrhoea.

The average age group of the children in the series was 1 year and 8 months and the causes of the diarrhoea fell roughly into five groups: (1) proved bacillary dysentery; (2) enteric infections where salmonellae, *B. proteus*, or *B. paracolon* were isolated on stool culture; (3) enteric infections with no pathogenic organisms on stool culture and no obvious parenteral infections; (4) parenteral infections; (5) mixed enteral and parenteral infections.

It was found that all three drugs were equally effective in cases where Shigella organisms were isolated from the stools and gave similar results in the enteric infections of non-dysenteric origin.

If diarrhoea was found to be secondary to a parenteral infection or if mixed infections were present, sulphadimidine had a definite advantage in that, in many cases, it controlled both infections without additional chemotherapy.

Toxic reactions such as oliguria or anuria were not encountered with any of these drugs under trial, and no other undesirable side-effects were noticed.

The trial period for each drug was limited to seven days, by which time 68.2% of the cases on phthalylsulphathiazole, 69.1% on sulphadimidine, and 61.1% on sulphaguanidine were fit for discharge.

A point of considerable importance was the relatively high incidence of dual infections, showing that it was not enough to attribute the diarrhoea to an obvious parenteral infection or yet to conclude that the majority of cases would be dysenteric in origin, since the two might well coincide, with the symptoms of one sometimes overshadowing those of the other.

Therefore, in reviewing all aspects of the problem of diarrhoea in African children, and bearing in mind that not all cases are admitted to hospital or seen and treated by fully qualified medical personnel, it is essential to provide a regime of treatment which combines efficiency with ease of administration, simplicity, safety, and cheapness.

Since the "wide spectrum" antibiotics are not always available for routine use and the "non-absorbable" sulphonamides require the addition of penicillin or other antibiotics in the case of mixed infections, it is suggested that sulphadimidine could be used as a valuable general-purpose sulphonamide in the diarrhoeal diseases of African childhood.

My thanks are due to the Director of Medical Services, Kenya Colony, for permission to publish; to Dr. E. R. N. Cooke, Medical Research Laboratory, Nairobi, for the bacteriological work; and to the sisters and staff of King George VI Hospital, Nairobi, for their co-operation and help.

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CHRONIC RECTAL BLEEDING DUE TO MILK

BY

F. P. ANTIA, M.D.Bom., M.S.Ill., M.R.C.P.Lond.
Associate Physician, B. D. Petit Hospital; Consulting Gastro-Enterologist, Tata Memorial Hospital and B. J. Wadia Hospital for Children, Bombay

AND

S. H. COOPER, M.B., B.S.

The following case of rectal bleeding probably due to an allergy to milk may be found of interest.

Case Report

A woman aged 38 was admitted to the B. D. Petit Hospital, Bombay, on November 15, 1953, with a history of bleeding per rectum for the past seven years. She had been operated on for both internal and external piles about six and a half years previously. She had been passing two stools a day, semi-solid, with no evidence of mucus. Blood was passed every day either mixed with stools or after the act of defaecation as frank blood or blood clots. The bleeding was not related to straining. She had been under observation in different hospitals for long periods, but bleeding per rectum persisted. There was no previous history of dysentery or diarrhoea. Her menstrual history was normal at first, but for the last three years she had a loss every three or four months for two or three days. Her father had severe asthma, and her son had allergic rhinitis. The patient had been married for 18 years and had twins, a boy and a girl, aged 17. Her husband was short-tempered, and at times used physical violence; consequently her married life was not happy.

Physical examination showed a well-built woman. Her blood pressure was 135/90 mm. Hg. No abnormality was detected in the cardiovascular, alimentary, or respiratory systems. The liver and spleen were not palpable. Vaginal examination showed no abnormality. A blood count showed: haemoglobin, 75%; red cells 3,100,000; white cells, 8,200 per c.mm. (polymorphs 82%, lymphocytes 18%). The bleeding time, coagulation time, platelet count, prothrombin time, and fragility tests were within normal limits. Seven years ago, when the patient was admitted to the same hospital, malingering was suspected because her husband was not treating her well at home, and traumatic bleeding from the rectum was supposed to be her device to stay in hospital. This time, however, every stool passed was semi-solid with mucus and frank blood not too well mixed. Microscopical examination showed many red blood cells. Urine analysis, gastric analysis and barium meal examination showed nothing abnormal. A barium enema suggested colitis of the descending and the sigmoid colon.

On November 18 a sigmoidoscope was passed 10 in. (25 cm.). At 2½ in. (6.3 cm.) an ulcer ¾ in. (1.9 cm.) in diameter was seen. The base was not raised. There were multiple punctate haemorrhagic areas ¼ to 1/6 in. (6 to 4 mm.) in diameter, the intervening mucosa showing only slight exudation of mucus throughout and no congestion A smear from the mucous membrane did not show amoebae and the culture was negative for any pathogenic organism. Punch biopsy from the ulcerated area showed submucous infiltration with eosinophil and mononuclear cells.

Punctate haemorrhagic spots without evidence of inflammation of the colon suggested a diagnosis of allergy. Since the commonest allergen is milk (Antia, 1953), it was decided to exclude milk allergy. On November 20 the patient was put on fruit juice and water only. The bleeding per rectum stopped on November 22—according to the patient, for the first time in the last seven years. Two soft-boiled eggs were added on November 25 and biscuits on November 27,

without any passage of blood, either macroscopically or microscopically. On November 28, in addition, half a cup of milk with half a cup of tea twice a day was started, and on the 30th bleeding per rectum recurred, continuing until the milk was stopped on December 2. Then only fruit juice, soft-boiled eggs, biscuits, and mashed potatoes were given for two days, during which there was no bleeding. On December 5 three cups of milk were added to the diet, and next day bleeding recurred, and continued until December 8. Thereafter the patient was given the routine hospital diet except that milk was stopped in all forms: the bleeding did not recur. On December 16 sigmoidoscopy showed that the ulcer had completely healed and that the colon looked perfectly healthy.

It was decided to test the sensitivity of the skin to milk and to try to desensitize the patient by small doses. However, the husband was impatient to take his wife home and she was discharged with advice to start taking one drop of milk a day and to increase it daily by one drop, as advised by Andresen (1953). The patient reported again three and six months later, when she said that, by gradually increasing the amount of milk by one drop every day, she was able to take milk in her tea (she had not ventured to take a larger amount) and that the bleeding per rectum had stopped completely.

Summary and Conclusions

The case is described of a woman aged 38 with an unusual history of bleeding per rectum every day for seven years. Any possibility of malingering was dispelled by punctate bleeding all over the colon, which led to the belief that it was probably an allergic manifestation. Milk allergy was suspected.

All diet was stopped except fruit juice and water, and for the first time in seven years the bleeding stopped. Further tests showed that bleeding restarted whenever milk was given.

An apparent lag of 24–48 hours between bleeding and starting or stopping of milk might be explained by the products of milk digestion coming in contact with the mucosa of colon (Gray *et al.*, 1940).

The patient has apparently been desensitized to milk by gradually increasing the amount by one drop a day.

Our thanks are due to the Superintendent, B. D. Petit Hospital, for permission to publish this case

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A good year, continuing the progress of the last few years, is reported by the British Empire Leprosy Relief Association for 1954. Every request for financial help to build homes for child patients was met, and by the end of the year 1,916 children were in the care of Belra in 23 different centres. The policy for treating adults has been to concentrate on out-patient care rather than on enforcing isolation, because the application of sulphone treatment depends on early diagnosis, which out-patient care facilitates. Two rural centres have been established in Tanganyika, a nurse has been posted to Northern Nigeria and a worker to Southern Nigeria to open treatment clinics throughout these neighbourhoods, and the number of Belra men on the Gold Coast working with the Government has been increased from one to eight. Many cases still need institution treatment, and for these a pilot leprosarium and a Red Cross Hospital are due to be opened in Tanganyika. Research on leprosy and in the allied field of tuberculosis is being carried on with the co-operation of the East Africa High Commission and the Medical Research Council.

Medical Memorandum

Ischaemia of Lower Limb as Cause of Motor Accidents

In view of the appalling number of road casualties in this and other countries, and the constant search for remedies, it is thought that the case described here will be of interest. It illustrates a possible cause of motor accidents which is not widely recognized.

Case History

A lorry driver aged 58 was referred for medical examination because he had been involved in numerous minor accidents. The nature of these accidents suggested either that his eyesight was defective or that he was grossly careless. He denied any eye trouble, or that he was unfit in any other way. He attributed his accidents to "bad luck" or "bad judgment."

On examination he was a grey-haired, rather elderly-looking man. His visual acuity and colour vision were normal. The only abnormal physical signs were a grossly deficient blood supply to the right foot—the right dorsalis pedis and posterior tibial arteries being impalpable—and diffuse loss of sensation over the sole and medial four toes of the right foot.

After the examination he admitted that his foot occasionally felt numb, so that he was unable to feel the brake pedal or accelerator when he was driving. Henceforth he was not allowed to drive on the public highway, but only on his firm's private roads. His private doctor was told of the disability, but the patient was not referred to a hospital for further investigation.

Five months later his right big toe became septic after minimal trauma, and he was treated at a hospital casualty department. When he reported for work a few days later his toe was partly gangrenous; he was referred to another hospital, where he was admitted. Here he was found to have an inflamed swollen hallux with a slough of the top part of the nail-bed. The right dorsalis pedis and posterior tibial arteries were still impalpable; and there was impaired sensation over the sole of the foot, which was inconstant and disappeared when the foot was warmed. A radiograph showed bony destruction of the tip of the phalanx of the right hallux, but the results of other investigations were normal.

Subsequently the dead bone in the toe was excised, and after graduated exercises he was discharged. He was no longer allowed to drive.

Comment

Arteriosclerosis is so common and widespread a disease that cases similar to the one described are probably not uncommon; especially when so many old people are allowed to drive cars.

In this case it was thought that the impaired blood supply to the foot caused an ischaemic neuropathy. As Cohen (1954) has pointed out, patients with ischaemic nerve lesions can present with slipper anaesthesia of the foot, a delayed response to pain or pressure, or wasting and paresis of the intrinsic muscles of the foot. Recovery from an ischaemic nerve lesion is slow, and the sole of the foot may remain numb.

Doctors should bear in mind the potential liability of such patients to their employers, and their potential danger to the public if they are allowed to drive motor vehicles. Casualty officers should always look for peripheral vascular disease as a cause of chronic infection or ulceration of the feet and toes. A gangrenous toe is usually recognized as such; but the fact that it may indicate a major arterial block high up in the limb (Leriche, 1940) is not so widely appreciated.

F. L. DAVIES, M.B., F.R.C.S.

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Reviews

PHYSICAL SIGNS IN SURGERY

Demonstrations of Physical Signs in Clinical Surgery. By Hamilton Bailey, F.R.C.S., F.A.C.S., F.R.S.E. Assisted by Allan Clain, M.B., F.R.C.S. 12th edition. (Pp. 456+xii; illustrated. 38s. 6d.) Bristol: John Wright and Sons Ltd. 1954.

A book that has necessitated twelve editions and ten reprints and been translated into six languages must patently have exceptional virtues which have enabled it successfully to meet a great demand. Many successive generations of medical students have imbibed the teaching in Hamilton Bailey's *Demonstrations of Physical Signs in Clinical Surgery*, and there is no doubt that the present 12th edition (in which the author has been assisted by Allan Clain) will be even more popular. The reasons for this are to be found on any page of the book opened at random, for it will reveal, not only a concise description of a physical sign, but several very excellent and clear photographic illustrations of cases showing the sign or how it is elicited, and these have obviously been chosen with great care. How lavishly these illustrations are provided will be appreciated when it is recorded that there are no fewer than 681 of them in some 430 pages of letterpress.

Since the first edition was published colour reproduction has come into its own, and in the present edition there are, despite their great cost nowadays, a very large number of first-quality coloured illustrations; indeed, the publishers and printers are to be congratulated upon the truth of tint they have achieved, for it will go far to make the student feel that he has actually observed the cases. As it is quite impossible for a student to see examples of every condition during his curriculum, these illustrations form a very good and useful "second best."

At a time when eponymous designations are rather frowned upon by the pundits it is refreshing to find that the author commends their use; as he says in the preface, "In many respects this is an advantage, for an anatomico-pathological label is often cumbersome." But to enhance the mere name he gives in footnotes a few personal details; thus "Jean Martin Charcot, 1825–1893, Physician, Hôpital Salpétrière, Paris." I regard this as entirely admirable, the only small criticism being that, in the case of some contemporary names, signs which have long been widely known and practised but are often of untraced origin are attributed to writers who happen to have mentioned them in their contributions. Nevertheless it is delightful, and instructive, to read: "Pierre Charles Alexandre Louis, 1787–1872, Physician in Paris. Some consider that it is Antoine Louis (1723–1792), Surgeon to the Charité Hospital, Paris, and designer of the guillotine, to whom the angle of Louis should be attributed." The latter certainly has the support of *Gray's Anatomy*.

Altogether this is an excellent production which can be strongly recommended to the student, and perhaps also to those who have to teach him.

NORMAN C. LAKE.

MORAL ASPECTS OF MEDICAL PRACTICE

Morals and Medicine. By Joseph Fletcher. Foreword by Karl Menninger, M.D. (Pp. 243+xvii. 15s.) London: Victor Gollancz, Ltd. 1955.

In this book a professor of "pastoral theology and Christian ethics" faces some of the moral problems encountered in modern medical practice which, though they have given the Roman Catholic Church "furiously to think," are still largely ignored by other Christian denominations and by the medical profession in general. Most moral systems are, as the author points out, anchored to some form of religious belief (and for him to the Christian religion), but it is through personality (which is a unique quality in every human being) that we obtain, he maintains, our knowledge of the good. This book should therefore appeal to every practising doctor who believes that the conduct of medical practice must be based on moral principles.

Starting from this premise the author discusses the moral problems associated with contraception and sterilization; and exhibits little sympathy with Catholic doctrine. Indeed, he comes down clearly on the side of man's right to control parenthood, within reason, and to prevent sterility by artificial insemination when necessary, within the marriage bond. He even comes down on the side of euthanasia. Here, however, we cannot help feeling that, though he is well informed on medical matters, lack of first-hand experience of medical practice leads him to carry his argument too far. For he underrates the power of modern medicine to relieve pain and keep unconscious for long periods. Nor does he seriously discuss the growing problem (much more important than that of active euthanasia) of withholding the standard treatment for a disease when, in the doctor's judgment, it would merely prolong suffering. Further, his lack of medical experience is evident in his discussion on the patient's right to be told the truth—the part of his book which the average practising doctor will find much the most important. True that the truth should be told much more often than it is told. But so often what is the truth? Minor criticisms of this kind, however, should not be allowed to detract from the real value of this well-written book, which should be brought and thought about by as many practising doctors as can make the time to read it.

A. E. CLARK-KENNEDY.

CLINICAL ENDOCRINOLOGY

Clinical Endocrinology: For Practitioners and Students. By Laurence Martin, M.D., F.R.C.P., and Martin Hynes, M.D., M.R.C.P. Second edition. Foreword by Sir Lionel Whitby, C.V.O., M.C., M.D., F.R.C.P., D.P.H. (Pp. 253+ix; illustrated. 20s.) London: J. and A. Churchill, Ltd. 1954.

It is pleasing to see that a second edition of this excellent little book has now appeared six years after the first. The very comprehensive and concise survey of endocrinology has been brought well up to date by the inclusion of such topics as isotope methods of thyroid investigation and modern knowledge of adrenal function and dysfunction. The boundaries of endocrinology continue to expand until they infiltrate deeply into most branches of medicine, and it becomes increasingly difficult to know where to draw its limits; but some must be drawn, and the authors of this book have wisely omitted any account of the many non-endocrine diseases for which cortisone or A.C.T.H. is useful.

A very great deal of reliable and up-to-date information is contained within these 250 pages, and more still can be obtained by use of the lists of references at the end of each chapter, which are up to date, well chosen, and to accessible journals. The illustrations also are informative and well selected. The result is a book of high standard which the publishers have produced at a low price. In a rapidly advancing subject such as this many aspects change frequently, but most of the information here presented is likely to remain valid for years to come.

The book is primarily designed for practitioners and for students working for higher degrees, and to both it can be recommended as an excellent survey of the subject in very handy form.

C. L. COPE.

Cargoes on the Great Lakes, by Marie McPhedran (George G. Harrap and Co., Ltd., 10s. 6d.), is a book of great charm that tells the story of the freighters moving on the face of the sea-waters of Lake Superior, Lake Michigan, Lake Huron, Lake Erie, and Lake Ontario, on whose hospitable shores many British doctors are now gathering with their Canadian cousins in the combined meeting of the Canadian Medical Association and the B.M.A. Marie McPhedran guides the reader along these great waterways with an intelligent hand, skilled in narrative and selection of points of interest; and Dorothy Ivens brightens the pages with the apt illustrations. A useful, enjoyable, and informative book for old and young.

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THE A.R.M.

Despite the difficulties of travel imposed by the railway strike there was an excellent attendance at this year's Annual Representative Meeting of the Association in the Great Hall of B.M.A. House in London under the chairmanship of Dr. I. D. Grant, of Glasgow. There were some 251 motions and amendments on the agenda, and the meeting, under able direction from the chair, completed its work by midday on Saturday, June 4, within the allotted space of three and half days. The Chairman, who, with his deputy, Dr. A. Beauchamp, of Birmingham, was returned to office unopposed for another year, may perhaps find the Representative Body less attentive to business when it moves its tents from the businesslike atmosphere of Headquarters to the attractions of seaside Brighton in 1956.

On the domestic front the meeting supported the Treasurer in his attitude of cautious optimism towards the Association's finances, and, in voting against suggestions for modifying the subscription rate for some categories of membership, agreed that after a period of stabilization time must be allowed to build up a reserve. The course of the debate also showed that representatives and their constituents continue to give anxious thought to the dangers of sectionalism within the profession and, correspondingly, the Association. As various speakers made clear, the Representative Body's desire to preserve its position as the effective parliament of the whole profession sprang as much from the need for professional unity as from a properly jealous regard for the Association's prestige. The Chairman of Council summed the matter up when he said " there was only one British Medical Association, which included all kinds and conditions of men, and its doors were open to all." All they had to do, he went on to say, " was to take their place as doctors among other doctors " in the affairs of the Association.

The meeting was unsympathetic towards some motions under the General Medical Services Committee's business calling for an increase in remuneration for general practitioners because of the increased cost of living. The chairman of the Committee, Dr. Talbot Rogers, had little difficulty in persuading his hearers that such ideas were out of touch with reality. But there was overwhelming support for a motion calling on the B.M.A. to continue to press for the right of private patients to receive drugs free of charge as part of the National Health Service. Several speakers rebutted the suggestion in the Cohen Report—and echoed by one sincere but solitary representative—that this provision would lead to two standards of practice. Dr. R. Green (Brighton) had the ear of the meeting when he urged that the essence of this matter was justice to the patients, of whom " some of the most impecunious have elected to remain private patients." In Dr. Rowland Hill's regretted absence through illness, Mr. Nicholson-Lailey took the bowling for the consultants and specialists and at the end of a long and patient innings received a well-deserved ovation.

The proposed ban of heroin by the Government came under fire after lunch on the third day of the meeting. The main burden of the protests in several motions and amendments was that the Association, as representing all branches of the profession, should have been consulted by the Government before taking action ; that if heroin was to come under a ban it should apply only to its export ; and that the banning of any drug of therapeutic value of whatever kind was a threat, even if a veiled one, to clinical freedom. Statesmanlike pleas from Dr. J. G. M. Hamilton and Dr. S. Wand that representatives should give due weight to the grave international aspects of the problem were attentively listened to, but the meeting registered by a majority its opinion that heroin should continue to be manufactured in this country, but not exported, and instructed the Council to approach the Government to seek a reversal of its decision.

Members of the public health service, disappointed by the recent award of the Industrial Court, should be heartened by the evident sympathy of the Representative Body. Dr. J. B. Tilley, chairman of the Public Health Committee, said that it was a matter of grave concern that medical men and women who chose to practise preventive medicine were paid less than they might expect to be paid in other branches of the profession. Speaking in the debate which followed, Dr. Guy Dain said that the first step in any medical service was the establishment of a preventive service, yet the reward offered to those in the public health service was so poor that young doctors were not coming forward to take the D.P.H. " We must do what we can to get them better conditions," Dr. Dain concluded, and the meeting passed a motion by Gateshead demanding urgent action to bring " remuneration in the salaried medical services of the

State and local authorities" up to a level comparable with that of the rest of the profession engaged in hospital and general practice.

One of the last matters to be discussed was the possibility of changing the arrangements at Annual Meetings, so that the Scientific Meeting and the Representative Meeting might be combined, thus enabling all members to have an opportunity of taking part in both the scientific and medico-political activities of the Association. Speakers recognized that this presented great difficulties, but the general opinion was that the suggestion was a useful one and well worth further investigation.

Though there were no fireworks this year, the A.R.M. dealt with the matters before it in a business-like way and much was achieved. The long hours of discussion were lightened by many pleasant social occasions, and by the labours of those who had the responsibility of arranging the meeting. In particular, thanks are due to the council of the Metropolitan Counties Branch, the Ladies Committee of the Branch, and the London Association of the Medical Women's Federation.

CORONARY DISEASE IN INFANCY

It has become evident that coronary thrombosis in young people is not so rare a disease as was previously thought.[1 2] In 1942 N. Reitman, W. R. Greenwood, and J. H. Kler[3] described 221 cases of coronary thrombosis in patients under 40 years of age, 34 being under 30 years of age. However, coronary artery disease was thought never to occur in infants until J. H. Bryant and W. H. White[4] described a case in 1891. Since then about forty cases in infancy and childhood have appeared in the literature. The frequency of recent reports of coronary artery disease[5-7] in young infants would suggest that arteriosclerosis and coronary thrombosis are not a natural process of ageing and "wear and tear," but due to some specific disease. The aetiology remains obscure, but infection, hyperparathyroidism, excess vitamin D, and inborn errors of calcium metabolism, such as idiopathic hypercalcaemia, have been suggested. Other possibilities that have been considered are drug therapy, rheumatic arteritis, allergy, and congenital abnormality of the arteries.

Pathologically, the findings in infants have been well tabulated and described.[6 8 9] Many of the medium-sized arteries are affected. Calcification occurs in the internal elastic lamina of the media, with subsequent fibroblastic proliferation of the intima. In some cases, calcification follows necrosis and granulomatous proliferation.[10] Myocardial damage consists of subendocardial infarction, patchy replacement fibrosis, and often subsequent calcification. In contrast to the condition in adults, atherosclerosis is extremely rare. Most of the infant patients have been between 2 and 8 months of age. One case was reported[11] with myocardial infarction occurring at 10½ hours of age, and W. A. Stryker[8] refers to abnormal vascular findings in a stillborn foetus.

Clinically, dyspnoea and pallor develop suddenly in a previously healthy infant; however, this acute picture may be preceded by intermittent vomiting and failure to thrive, or merely by a mild upper respiratory infection. On physical examination the child's condition closely resembles that of adults with myocardial infarction. Dyspnoea, shock, ashen-grey colour of the skin, and evidence of cardiac failure are prominent findings. Pulmonary oedema and hepatic enlargement are frequently present. Clinically and radiologically the heart is grossly enlarged. W. A. Cochrane and D. H. Bowden[6] suggested that radiography of the neck might aid in the diagnosis by revealing calcification of the thyroid arteries, which are commonly affected. Few electrocardiograms have been done, but these are often typical of ventricular hypertrophy, myocardial anoxia, and infarction. Death is usually rapid—a matter of a few hours.

The differential diagnosis would include those conditions producing sudden collapse in young infants. Hence fulminating septicaemia, adrenal insufficiency, and congenital renal disease could be diagnosed by the usual diagnostic procedures. Certain congenital cardiac conditions which give rise to cardiac failure in young infants, such as patent ductus arteriosus, coarctation of the aorta, and transposition of the great vessels can be distinguished without much difficulty by present-day methods. However, endocardial fibroelastosis, acute interstitial myocarditis, and glycogen storage disease of the heart all produce marked cardiac enlargement and failure in young infants, and would be almost impossible to differentiate. Moreover, an aberrant left coronary artery from the pulmonary artery gives a similar clinical and electrocardiographic picture. Treatment has been very disappointing and the fact that the diagnosis has most commonly been made at the post-mortem table testifies to the inefficacy of oxygen, antibiotics, digitalis, mercurial diuretics, and the other drugs that have been tried.

1 French, A. J., and Dock, W., *J. Amer. med. Ass.*, 1944, **124**, 1233.
2 Zacks, L., *Amer. Heart J.*, 1943, **26**, 269.
3 Reitman, N., *et al.*, *Amer. J. med. Sci.*, 1942, **203**, 792.
4 Bryant, J. H., and White, W. H., *Guy's Hosp. Rep.*, 1901, **55**, 17.
5 Nestor, J. O., *et al.*, *Clin. Proc. Child. Hosp.* (*Wash.*), 1953, **9**, 11.
6 Cochrane, W. A., and Bowden, D. H., *Pediatrics*, 1954, **14**, 222.
7 Martelle, R. R., *J. Pediat.*, 1955, **46**, 322.
8 Stryker, W. A., *Amer. J. Dis. Child.*, 1946, **71**, 280.
9 Brown, C. E., and Richter, I. M., *Arch. Path.* (*Chicago*), 1941, **31**, 449.
10 Lipman, B. L., *et al.*, *Amer. J. Dis. Child.*, 1951, **82**, 561.
11 Ravich, R. M., and Rosenblatt, P., *J. Pediat.*, 1947, **31**, 266.

CAUSE OF ITCHING

Since the work of Sir Thomas Lewis showing that a substance indistinguishable from histamine existed in a combined form in human skin, that histamine was liberated when the skin was damaged, and that histamine pricked into the skin caused itching, the view has been widely held that itching of the skin is due to the release of histamine. The view gained support from the observation that antihistamine substances relieved the rash and the itch of urticaria. Two years ago J. L. Broadbent[1] published an account of work with cowhage, which is the name given to the trichomes which cover the pod of a tropical plant, *Mucuna pruriens*. Cowhage is sometimes sold as itching powder, and it has been believed to cause itching mechanically. However, Broadbent came to the conclusion that cowhage caused a liberation of histamine in the skin, though cowhage itself did not contain histamine, as nettle stings have been shown to do.[2] He based his conclusion on the observations that extracts of cowhage produced a triple response (like histamine) when injected intradermally, that when cowhage was first extracted, the material left behind caused little itching, and that an antihistamine substance given by mouth reduced the itching caused by cowhage. Subsequently K. Bowden, B. G. Brown, and J. E. Batty[3] showed that a crude extract of the trichomes of cowhage contains 5-hydroxytryptamine, and the authors stated that this substance probably accounts for the pain which occurs when cowhage is applied to the skin, though they could not say whether it was responsible for the itching.

Now comes a further development in a publication by R. P. Arthur and W. B. Shelley.[4] They claim that the active principle in cowhage which causes itching is an enzyme called mucunain, and have described the results of testing a series of enzymes for their power to produce itching. They used the trichomes of cowhage to introduce these enzymes into the skin after first destroying the mucunain by "autoclaving at 250° C. for 30 min." They then soaked the trichomes in the enzyme solutions, which ranged in strength from 10% downwards. They found that when they introduced a single impregnated trichome into the skin, using a watchmaker's forceps and working under a microscope, a localized itch resulted which was "mild to intense." They tried a wide variety of enzymes, and found that only proteinases were active, and of these only the endopeptidases with activities in the physiological *p*H range. Thus among the active ones were papain, trypsin, and chymotrypsin, while pepsin and many others were inactive. The three active enzymes were studied as crystalline preparations; they caused itching with the shortest latent period (5 sec.) and the longest duration (30 min.). Arthur and Shelley believe that these enzymes cause itching by liberating another substance, but they believe that this is not histamine. Their reason for this is that the active endopeptidases invariably elicited the pure sensation of intense itching without any weal or flare, whereas histamine and the potent histamine liberator 48/80 never produced itching in the absence of wealing.

[1] Broadbent, J. L., *Brit. J. Pharmacol.*, 1953, **8**, 263.
[2] Emmelin, N., and Feldberg, W., *J. Physiol.*, 1947, **106**, 440.
[3] Bowden, K., *et al.*, *Nature* (*Lond.*), 1954, **174**, 925.
[4] Arthur, R. P., and Shelley, W. B., ibid., 1955, **175**, 901.

B VITAMINS IN TOXIC STATES

Replacement therapy in actual or threatened deficiency states is the only theoretically valid indication for vitamins of the B complex. The average diet in this country contains ample vitamin B to meet nutritional requirements, and deficiency syndromes are very rare. When they occur, they are nearly always caused by defects of absorption such as the steatorrhoeas, the disorders which may follow gastro-intestinal surgery, or pernicious anaemia, which is due to a failure to absorb vitamin B_{12}. Vitamin-B deficiencies are difficult to induce in man, and prolonged deprivation is usually necessary. It is several years before vitamin B_{12} deficiency becomes manifest after total gastrectomy, which removes the natural source of intrinsic factor; and clinical signs of pyridoxine deficiency cannot be deliberately induced in man unless a metabolic antagonist to the vitamin is given.[1] It is therefore unlikely that true deficiencies can arise in acute toxic states, and if the B vitamins have any beneficial effect it is probably due to some secondary action analogous to the vasodilator effect of nicotinamide. Thiamine and pyridoxine have long been popular in the treatment of radiation sickness, vomiting of pregnancy, and postoperative vomiting. Pyridoxine has been the more frequently used, but even in controlled trials the results have been conflicting,[2 3 4] although response has been more convincing in radiation sickness than in other forms of nausea and vomiting.[5] There is some evidence that patients with vitamin-B deficiency are abnormally sensitive to irradiation.[6] Intravenous thiamine and pyridoxine have also been used empirically in the treatment of acute alcoholism.[7 8] Nausea, vomiting, and anorexia are difficult symptoms to assess objectively, and a convincing answer can only come from large-scale blind trials in which neither patient nor doctor knows whether test substance or dummy is being used. If clinical impressions could be confirmed in this way it would not be the first time that successful treatment has been based on doubtful premises.

Vitamins of the B group have also been used in the treatment of acute and chronic liver disease. In cirrhosis of the liver they are indicated only in patients with alcoholism and associated malnutrition: in infective hepatitis their value has never been convincingly demonstrated. Campbell and Pruitt[9] recently carried out a

[1] Vilter, R. W., *et al.*, *J. lab. clin. Med.*, 1953, **42**, 335.
[2] Bergmann, W., *Canad. med. Ass. J.*, 1947, **56**, 554.
[3] Kernis, L., and Stodsky, B., *Anaesthesia*, 1950, **11**, 212.
[4] Hesseltine, H. C., *Amer. J. Obstet. Gynec.*, 1946, **51**, 82.
[5] Ellis, F., and Stoll, B. A., *J. Fac. Radiol.* (*Lond.*), 1951, **3**, 207.
[6] Bean, W. B., *et al.*, *Amer. J. med. Sci.*, 1944, **208**, 46.
[7] Wordsworth, V. P., *British Medical Journal*, 1953, **1**, 935.
[8] Martensen-Larsen, O., ibid., 1954, **2**, 464.
[9] *Amer. J. med. Sci.*, 1955, **229**, 8.
[10] *Ann. intern. Med.*, 1954, **41**, 963.
[11] *British Medical Journal*, 1950, **2**, 748.
[12] Ibid., 1955, **1**, 459.

controlled trial of vitamin B_{12} and folic acid in soldiers with infective hepatitis and claimed quicker clinical recovery and more rapid improvement in liver function tests in the treated group, but Colwell[10] was unable to confirm this. Latner[11] includes B vitamins in the treatment of acute liver failure, but Reynell[12] has shown that they are of no value in experimental liver failure in rats, and there is little theoretical justification for their use. It has yet to be shown that vitamin B therapy has any place in the treatment of liver disease as it is seen in this country.

ADVERTISING ON TELEVISION

The Independent Television Authority published last week a booklet entitled "Principles for Television Advertising" which is described as a general code of television advertising conduct. The rules are based on the recommendations of a committee appointed by the Authority, the Advertising Advisory Committee, on which Dr. Guy Dain serves as a representative of the British Medical Association. The general principle which will govern all television advertising is that it should be "legal, clean, honest, and truthful." It follows that false and misleading advertisements will not be allowed, and "no advertisement shall contain any reference which is likely to lead the public to assume that the product advertised has some special property or quality which is in fact unknown, unrecognized, or incapable of being established." Scientific terms must be used with a proper sense of responsibility to the ordinary viewer, and the irresponsible use of testimonials must be avoided. In so far as advertising on children's programmes is concerned, no product is to be advertised which might result in harm to children physically, mentally, or morally, and no method of advertising may be used "which takes advantage of the natural credulity and sense of loyalty of children." Among the particular safeguards specified is one which forbids any advertisement which encourages children to enter strange places or to converse with strangers in an effort to collect coupons, wrappers, or labels.

The advertising of medicines and treatments presents particular problems. The rules state that no advertisements will be accepted for specifics for slimming or bust development, contraceptives, smoking cures, and products for the treatment of alcoholism. In addition there are already statutory restrictions on the advertising of remedies for cancer, venereal diseases, tuberculosis, and other disorders. In general, advertisements for medicines will be accepted if they comply with "The British Code of Standards in Relation to the Advertising of Medicines and Treatments." This code,[1] which has the approval, among other bodies, of the Newspaper Proprietors Association, the Advertising Association, and the Proprietary Association of Great Britain, has helped greatly in recent years to improve the standard of patent medicine advertisements in newspapers and periodicals, and its strict application to television advertisements should be a useful safeguard against any tendency to unscrupulous advertising of medicines or methods of treatment. Finally, doctors will be relieved to know that "statements, gestures, or representations that give the impression of professional advice or recommendation should not be allowed."

[1] "British Code of Standards in Relation to the Advertising of Medicines and Treatments," 1953, third edition.

SHOPLIFTING

Only very few of the many convicted shoplifters are referred to the psychiatrist. In the course of one year 3,400 persons were apprehended for shoplifting in five Chicago department stores; 4.5% were arrested, and for 25 of them psychiatric opinion was sought because they appeared to suffer from mental symptoms. Of 338 cases of shoplifting referred to a Chicago psychiatric institute,[1] 313 were females. 77% were labouring under a definable nervous disorder. Almost all psychiatric conditions were represented, mild depressions being the most frequent. Kleptomania (compulsive stealing) was found only in 4% of the group. Shoplifting was not related to economic status.

At a recent meeting of the Medico-Legal Society, Lindesay Neustatter[2] discussed some interesting cases of shoplifting. He pointed out that, contrary to generally held beliefs, "of all crimes, theft is at the same time the simplest and the most difficult to understand."[3] The association of shoplifting with tension and sometimes with sexual excitement has been known for a long time. It has been found to be precipitated by unfulfilled craving for affection and by lack of sexual gratification. In each of Lindesay Neustatter's five cases the irrational theft had taken place in a state of tension and depression. Three of his patients showed evidence of an hysterical personality. In one of his cases the act of shoplifting had been preceded by a craving for sweets, which had resulted in an excessive gain in weight. This case recalled J. Wilder's[4,5] account of shoplifting in states of spontaneous hypoglycaemia. In the view of many psychiatrists the abnormal behaviour of the offenders does not imply that they should necessarily get away without punishment.

Regrettably, there is little systematic knowledge about shoplifting as a neurotic symptom. The offence has become more frequent since the barriers between potential customers and the goods they are invited to buy have been completely removed in many places. Some people find buying things a pleasant relief in states of depression, and a similar mechanism, though more primitive, might be at work in shoplifting, where the mode of acquisition provides an added thrill. The coexistence of this abnormal manifestation of acquisitiveness with oral craving recalls a similar association among the so-called oral character traits. There is need for more systematic studies in this field. It might even pay the big department stores, which are the chief victims of this offence, to finance serious research into this problem.

[1] Arieff, A. J., and Bowie, C. G., *J. clin. Psychopath.*, 1947, **8**, 565.
[2] Neustatter, W. L., *Med.-leg. J. (Camb.)*, 1954, **22**, 107.
[3] —— *Psychological Disorder and Crime*, 1953, London.
[4] Wilder, J., *J. crim. Psychopath.*, 1940, **1**, 219.
[5] —— *Correctional Psychology*, 1944, New York.

PROLONGED PREGNANCY

The question of postmaturity arises often enough to perplex the obstetrician, and the question of how long a live pregnancy can remain in the uterus is of considerable medico-legal importance. Attention might therefore be drawn to a short paper recently published by Burrows,[1] in which he discusses the possibility that delayed nidation of the fertilized egg might account for some cases of prolonged gestation in the human. He points out that for some time biologists have known that blastocysts do not need an immediate attachment to the uterus for their survival. Most of the pertinent observations have been made on rodents. In mice gestation may be retarded by injury soon after coitus or by the occurrence of conception during lactation. But in other rodents, and perhaps in seals, delayed nidation is said to occur normally and in the absence of adverse factors, the blastocyst lying dormant for months before the development of the embryo is resumed. Further, Burrows himself noted that mice and rats occasionally bore two successive normal litters after a single mating. The explanation is said to lie in the retention of some of the blastocysts in the oviducts, their survival in a dormant state throughout pregnancy, and their subsequent entry into the uterus to develop as a second litter.

The possibility of deferred nidation occurring in the human raises several points of interest. It might explain cases of alleged superfoetation, either when twins of unequal maturity and size are born together, or the even rarer cases in which two babies of equal maturity are born within a few months of each other. It might also explain those cases in which, despite pregnancy being prolonged as measured by our present criteria, the foetus shows no signs of postmaturity either before labour or at delivery. One way of studying the question might be to make inquiries among women who became pregnant during lactation to see if the date of their conception could be determined accurately perhaps because of a single act of coitus. If the average interval between conception and delivery were found to be lengthened in these cases, it might afford relevant evidence.

[1] Burrows, H., *J. Obstet. Gynaec. Brit. Emp.*, 1954, **61**, 762.

PLEASE REPLY TO THE G.M.C.

Although the necessity for "getting registered" is well understood it is not so generally realized that, disciplinary procedures apart, it is occasionally necessary for doctors to take steps to keep registered. On two occasions[2 3] last year reminders to readers of the liability to erasure from the *Register* under the provisions of Section 14 of the Medical Act were published in the *Supplement*. Section 14 makes it the duty of the Registrars of the General Medical Council to keep the *Register* correct and "to erase the names of all registered persons who shall have died and . . . from time to time make the necessary alterations in addresses or qualifications of the persons registered." To carry out this duty the Registrars are empowered to write a letter to any registered doctor to inquire whether he has ceased to practise or has changed his residence; and the Act goes on to say that if there is no answer to such a letter within six months "it shall be lawful to erase the name of such person from the *Register*." Some such powers as these are necessary if the General Medical Council—the body responsible for keeping the *Register*—is to carry out its essential task. A register which continued to include the names of deceased practitioners would fall into disrepute, not to mention the increased risk of impersonation which is sometimes attempted.

A letter at page 286 of this week's *Supplement* shows that at least one doctor is not clear about the procedure used by the Registrars in carrying out their obligations. At the beginning of each year about 10,000 doctors' names are selected alphabetically from the *Register* (the intention is to cover the entire *Register* in cycles of about five years), and they are circularized from the offices of the Council in London and Edinburgh by ordinary post with a request for confirmation of the correctness of the details already recorded on the *Register*. A detachable form is enclosed for reply. According to the President of the G.M.C.[4] in one year one-third, and in no year less than one-sixth, of the practitioners circularized do not reply to this letter. A further—and registered—letter is sent in June to those practitioners who fail to reply to the first letter. During the summer and autumn the Council attempts to trace the practitioners who have not replied to either letter (and are therefore becoming liable to erasure) by seeking fresh addresses from the British Medical Association, the medical protection societies, the *Medical Directory*, and other sources. As a result of the co-operation, entailing not a little labour, of the bodies and persons consulted, the Registrars are usually able to establish communication with all except about 500 of the practitioners in question. In November or December of each year the names of the practitioners with whom it has not been possible to establish contact are erased.

Early in the present year every practitioner originally registered by virtue of an English, Scottish, or Irish qualification (other than a practitioner who became fully registered after January 1, 1954) whose name begins with a letter between I and N inclusive should have received a letter sent on behalf of the Council. Letters are not sent in the normal course to provisionally registered practitioners. Further registered letters were sent in May to practitioners who did not reply to the original letters. Any practitioner who has received a letter from the Council and has not replied would therefore be well advised to communicate with the appropriate office of the Council.

Medical men are supposed to be lax in filling up forms, replying to questionaries, and so forth. It seems to be an occupational hazard. But it requires little imagination to see that the elaborate efforts made to trace the missing thousand or two names each year cost a great deal in time, money, and patience. Common courtesy, as well as self-interest, surely demands a prompt answer to the Registrars of the G.M.C.

[2] *Supplement*, January 2, 1954, p. 4.
[3] Ibid., October 16, 1954, p. 142.
[4] *Supplement*, June 4, p. 267.

EMERGENCIES IN GENERAL PRACTICE

PULMONARY EMBOLISM

BY

R. B. HUNTER, M.B.E., M.B., Ch.B., F.R.C.P.Ed., M.R.C.P.

Professor of Pharmacology and Therapeutics, University of St. Andrews, Queen's College, Dundee

Pulmonary embolism is thought to be the cause of death in 3% of hospital patients who are examined *post mortem*, but in only one-third of these is the diagnosis made before death. This fact stresses the difficulty in making the diagnosis of this serious and often fatal condition. In a significantly large number of cases pulmonary embolism is not the sudden dramatic incident of acute dyspnoea, chest pain, and circulatory collapse.

Aetiology

The one condition which is essential for pulmonary embolism is that a clot should form in any portion of the cardiovascular system peripheral to the pulmonary artery, and parts of this become detached and be carried by the blood stream into the pulmonary tree. The vast majority of emboli actually come from the deep veins of the legs, some from the pelvic veins, a few from the right side of the heart or from the venous channels in the upper extremities. The facts which are known about the disease are that it occurs principally in patients strictly confined to bed, and that it is rare in patients under 30 years of age. It is as common in medical as in surgical cases, with a notably high incidence among those with heart disease, though in 90% of these the origin of the clot is in the peripheral veins.

Two factors seem to be important in the initiation of deep vein thrombosis, one is slowing of the blood stream, and the other is injury to the vessel wall. Rest in bed produces slowing of the blood stream. Congestive heart failure also results in slowing of the circulation, and when due to mitral stenosis or myocardial infarction appears to be particularly apt to lead to venous thrombosis. Injury to the vessel wall may be of recent origin as in trauma, or there may be chronic insufficiency of the calf veins with distortion and dilatation of the venous channels. Such a state of affairs occurs temporarily during pregnancy, and predisposes the patient to thrombosis.

A small group of cases do occur in apparently healthy, ambulatory individuals, many of whom have recurring episodes of calf-vein thrombosis. It is said that this group, which is rare, is composed predominantly of males, but in my experience these patients are equally often females. Nearly one-third of them develop pulmonary embolism, and when this state of affairs occurs in ambulant patients it is important to consider the possibility of neoplastic disease and thromboangiitis obliterans.

Four events may result from sudden obstruction of the blood flow in the pulmonary arterial system: (1) the development of pulmonary infarction due to the obstruction; (2) the development of acute cor pulmonale because of a sharp rise in right ventricular pressure; (3) peripheral vascular collapse; and (4) the onset of certain cardiac disorders. It must be stressed, however, that pulmonary infarction, cor pulmonale, or cardiac disorders may occur without any dramatic incident. Anoxia may also result and be of sudden or gradual onset in any particular case.

Clinical Picture

The clinical features in any patient with this condition depend on the preponderance of the different factors mentioned, the size of the vessels occluded, movement of the emboli within the pulmonary vessels, and the state of the heart and lungs prior to the onset.

Pain may be due to disturbances in the pulmonary circulation, to pleural involvement, or to impairment of the coronary circulation. Fortunately from the diagnostic point of view, chest pain occurs in 75% of cases, in two-thirds of which it is pleuritic in nature, because of involvement of the pleura overlying the infarction, and in one-third anginal. It has been claimed that the latter is due to reduced coronary blood flow.

Fever occurs in over two-thirds of the patients and a sharp rise of temperature associated with leucocytosis may suggest a diagnosis of pneumonia. The fever does not, however, respond to the administration of antibiotics. Occasionally fever is the principal clinical manifestation of pulmonary embolism, perhaps associated with minimal chest signs on auscultation and a radiograph which is passed as normal.

Breathlessness may result from bronchospasm, immobility or diminished respiratory excursion of the diaphragm, anoxia, pulmonary infarction, or impairment of cardiac function, but it is important to remember that breathlessness may not be present.

Physical signs in the lungs may be absent in spite of chest pain and breathlessness, or, on the other hand, a massive area of infarction associated with a large pleural effusion may dominate the clinical picture, and if, as often happens, the pleural fluid is blood-stained, the diagnosis of pulmonary neoplasm may be entertained.

Cough is almost as common as dyspnoea, occurring in one-third of the patients, but haemoptysis, which is thought to be one of the classical features, is evident in only one-quarter of the cases.

Occasionally the presenting picture is one of acute cor pulmonale without any history of deep venous thrombosis or complaint of chest pain or haemoptysis. Under these circumstances there may be prominent pulsation over the pulmonary artery, dilatation and pulsation of the jugular veins, and cyanosis. In these cases a loud pericardial friction rub may be heard over the pulmonary area. This clinical picture may persist for days or weeks, or may be transient, particularly if right heart failure supervenes. Paroxysmal auricular fibrillation, paroxysmal auricular tachycardia, high-grade auriculo-ventricular block, and bundle-branch block may occur as part of the clinical picture.

Sudden chest pain and fever are therefore the commonest presenting features of pulmonary embolus and may on occasion be found without any other symptoms or signs. The diagnosis may be obvious or very difficult. I recently attended the post-mortem examination of a patient who was twice in my wards with "pneumonia." Pulmonary embolism was suspected because the response to antibiotics was unsatisfactory, but no confirmatory evidence could be found on detailed clinical, radiological, or cardiographic examinations. After her second admission she was sent to a convalescent home, where she died suddenly from a massive embolus. At post-mortem examination a solid clot extended from the deep calf veins to the inferior vena cava.

In the physical examination of the case of suspected embolism care has to be exercised, and on no account should the patient be asked to breathe deeply to facilitate auscultation of the chest. Death has occurred under such circumstances following the sucking of a large clot into the chest. The administration of adequate laxatives is also important to avoid straining at stool.

It will be evident from this account that the clinical picture may simulate many other disorders, more commonly pneumonia, acute myocardial infarction, pleurisy with effusion, pulmonary neoplasm, acute heart failure, or asthma.

Electrocardiographic examination is of great value in distinguishing acute pulmonary embolism from myocardial infarction, particularly when the patient complains of substernal pain. In pulmonary embolism there is usually electrocardiographic evidence of acute right ventricular stress. The changes are maximal within the first three days and may persist for weeks. In 15% of cases there is transient right bundle-branch block, making differentiation from myocardial infarction very difficult. A normal electrocardiogram, however, does not exclude pulmonary embolism.

Radiological Examination of the Chest.—When embolism occurs without infarction there may be a segmental area of increased translucency owing to absence of vascular shadows in the ischaemic area. Rounded or wedge-shaped shadows may be visible when infarction occurs. There may be no radiological signs or a massive area of consolidation. Radiological signs are so variable that I doubt the wisdom of moving a patient in domiciliary practice for this examination alone.

Diagnosis and Prognosis

It is obvious that a massive pulmonary embolus occurring without warning or signs of deep vein thrombosis cannot be anticipated and prevented. In my experience, however, more than half the cases which develop a pulmonary embolus have symptoms or signs before the major accident which are disregarded, some by the patient—such as pain in the calf; some by his medical attendant—unexplained pyrexia, slight chest pain, or a short attack of breathlessness—because many physicians still hesitate to consider the diagnosis without severe breathlessness, chest signs, and haemoptysis. The realization that pulmonary embolism may occur without dramatic symptoms and signs is all-important, and in such patients anticoagulant therapy should be instituted when deep vein thrombosis or a small pulmonary embolus is *suspected*. All seriously ill persons should have regular and frequent examinations of the calves for tenderness.

Published results suggest that 40% of patients who experienced a minor incident had a major embolism, and half of them died before the institution of anticoagulant therapy. In my experience, 18% of patients who had an embolus had a second one in spite of adequate anticoagulant therapy. The death rate in these treated cases was, however, greatly reduced, being in the region of only 2%. Anticoagulant therapy is therefore a major advance in the treatment of pulmonary embolism.

Treatment

Cases fall commonly into two clinical groups from the point of view of treatment. (1) The small embolus associated with chest pain, some rise of temperature, and perhaps slight breathlessness. Morphine, 15–20 mg. (¼–⅓ gr.), should be given initially by subcutaneous injection to allay distress and anxiety and anticoagulant therapy instituted. If such cases are not treated there is a risk of a second major embolus and also the danger of extension of the clot in the pulmonary tree giving rise to the gradual development of cor pulmonale or a large area of infarction without any further major incidents. Many cases in this category are diagnosed as pneumonia and are found resistant to treatment for that condition. (2) A large embolus, producing shock, acute breathlessness, pleural or substernal pain, cyanosis, and a fall of blood pressure. Morphine, 20 mg. (⅓ gr.), and atropine, 1 mg. (1/60 gr.), should be given by subcutaneous injection immediately and heparin is also urgent (see below). Morphine, 15 mg., may be repeated in one hour if considered necessary. Oxygen therapy is indicated if anoxia is marked.

Further treatment depends on developments. The patient may require treatment for cardiac failure or the intravenous injection of 0.5 g. of aminophylline for bronchospasm. In patients who have a large lung infarct it is wise to give antibiotics prophylactically.

When is it desirable to move the patient to hospital? Cases which have had a small embolism without shock or collapse can usually be moved at any convenient time, but they should be under the influence of heparin when this is done. Those who have suffered a massive embolism with shock and circulatory collapse are not fit to move. The temptation must be resisted to rush these cases to hospital for anticoagulant treatment. Difficult though the treatment may be to carry out in the home, therapy as detailed below should be carried out there until the patient is sufficiently recovered to withstand the stress of the journey.

Anticoagulant Therapy

Heparin is the drug of choice for the initial treatment of pulmonary embolism, and 15,000 units should be given intravenously by the practitioner whenever the diagnosis is made, and 10,000 units at six-hourly intervals thereafter. It is safe to administer heparin in this way, and control clotting times are unnecessary. Heparin prevents extension of the clot and promotes its resorption; it also has a vasodilator action. Its administration should be continued for three to five days. At a suitable time during this period the patient should be transferred to hospital for coumarin therapy. Heparin is of less value than coumarin-type anticoagulants in producing recanalization in the thrombosed vessel, both in the lungs and in the deep calf veins. It is unfortunate that coumarin treatment requires laboratory control, but it can be perfectly well carried out in the home if the laboratory facilities are at hand.

On the last day of heparin treatment 100 mg. of phenylindanedione (P.I.D.) should be given twice by mouth. The following morning the one-stage clotting test* is carried out, and further dosage of P.I.D. determined. During the first week of P.I.D. therapy daily estimations by the one-stage clotting test are required, but thereafter weekly or fortnightly estimations are usually sufficient. Over 70% of patients are maintained satisfactorily with a dose of 50 mg. a day. In the cases in which there are no further complications therapy should be continued till the patient has been fully ambulant for about a week or until there is resolution in the area of pulmonary infarction. The most remarkable improvement often occurs in an area of lung apparently irreparably damaged. When there is persistence of lung signs or evidence of acute cor pulmonale, treatment may have to be continued at home or in hospital with weekly laboratory checks for months. Some of our patients who required six to eight months' treatment have made a complete functional recovery.

In cases with recurrent pulmonary emboli, particularly when associated with mitral stenosis or migrating thrombophlebitis, permanent out-patient anticoagulant therapy should be considered.

Contraindications to Therapy.—Anticoagulant therapy is contraindicated under the following circumstances: if the patient is known to have a duodenal ulcer, malignant disease, advanced hepatic or renal disease, or any bleeding diathesis. It is also probably wise to avoid this form of therapy in severe hypertension if there is a history of cerebral thrombosis or if cerebral embolism has occurred within the previous fortnight.

Prevention

Early ambulation after operation or illness is desirable. Breathing exercises and foot and leg movements should be carried out in all patients confined to bed. These need not be elaborate, can easily be carried out in the home, and do not require the supervision of a physiotherapist. Flexion

*Quick, A. J., Stanley-Brown, M., and Bancroft, F. W., *Amer. J. med. Sci.*, 1935, **190**, 501.

and extension of the ankle and knee-joints, together with clockwise and anticlockwise rotation of the feet, carried out two or three times a day is all that is required. In patients with a previous history of deep vein thrombosis, or thought to be likely subjects for thrombosis, knee-length elastic stockings should be fitted and worn during the period of bed rest. Thigh-length elastic stockings are undesirable because they wrinkle at the knee and may themselves traumatize the veins. Wilkins and his colleagues (*New Engl. J. Med.*, 1952, **246**, 360) have shown that this simple procedure is sufficient to increase the blood flow in the calf veins and reduce the incidence of thrombosis. Patients with a history of deep venous thrombosis who are too ill to carry out leg exercises efficiently should be given anticoagulant drugs prophylactically and the foot of the bed should be elevated. A superficial vein thrombosis is not an indication for anticoagulant therapy. In fact, such treatment is contraindicated when phlebitis is present. But it must be remembered that patients in this group may also have damaged calf veins and may develop deep thrombosis. In pregnancy it is almost certain that patients have abnormally dilated deep veins and a careful watch must be kept when superficial thrombosis occurs.

Next article on Emergencies in General Practice.—"Serum and Anaphylactic Reactions," by Dr. D. A. Williams.

Refresher Course Book.—Copies of the second volume of collected articles from the Refresher Course for General Practitioners are still available at 25s. (postage 1s.) each. The first volume is now sold out.

Clinical Pathology Book.—"Clinical Pathology in General Practice," a collection of 39 articles on clinical pathology that appeared in the *Journal* as part of the Refresher Course for General Practitioners, is now available, price 21s. (postage 9d.).

Both these volumes are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

THE QUEEN AT HAMMERSMITH HOSPITAL

To mark the jubilee of the Hammersmith Hospital and the twentieth anniversary of the inauguration of the Postgraduate Medical School of London, which is associated with it, the QUEEN paid a visit to both institutions on June 6. Her Majesty was received at the entrance to the hospital by the MINISTER OF HEALTH (Mr. Iain Macleod), and proceeded at once to the School, where she was first shown documents relating to its opening by George V in 1935, one of his last public engagements. She then proceeded to one of the wards, where postgraduate students, including those from the Commonwealth and Empire, were in attendance. Three special exhibits were inspected by Her Majesty. The first was the metabolic unit, built last year for the investigation of metabolic disorders, including the effect of radiation upon the human body. The second was the Medical Research Council unit, a new building containing besides research laboratories an 8-million-volt linear accelerator and a 45-in. (1.1-m.) medical cyclotron. The third was the exhibition illustrating the research work of the School in the fields of surgery, medicine, obstetrics and gynaecology, and pathology. In the surgery section a display which caught the eye was the artificial heart–lung machine. The effect of operation and anaesthesia on the circulation was also ingeniously shown. The medical exhibit included a mass spectrometer for the instantaneous analysis of respired gases. Another exhibit was designed to demonstrate advances in the treatment of hypertension with new drugs. In the pathology section there were displays of improved vaccines for the treatment of chronic staphylococcal infections, and of the mechanisms of inheritance and variation in bacteria. Finally, the Queen spent some time in the wards and paid a visit to the nurses' home.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

The Ban on Heroin

SIR,—The banning of heroin seems to have produced in your correspondence columns a good deal of heat without much light. On the one hand we have the decision of an international committee, composed of not inconsiderable clinicians and pharmacologists, including members of the Narcotics Commission of the U.S.A. whose exhaustive researches on the addiction problem entitle them to a careful hearing; on the other hand we have the conviction of a number of distinguished clinicians that heroin is sometimes the only effective analgesic. The path of therapeutics is strewn with rejected remedies once held to be of great clinical importance, but there has been more than one instance where hasty generalizations largely on negative evidence have led to the unjustified condemnation of a remedy. In two instances to which I am referring, cod-liver oil and liquid extract of ergot, clinicians persisted in using them, and eventually their effectiveness was objectively established by the discovery of the vitamin content of the first and the ergometrine content of the second. Heroin is, however, to be banned without evidence of the kind that could objectively establish whether the clinical impressions of your correspondents are soundly based or not. A final trial of an analgesic, as any pharmacologist who has worked with them knows, can only be carried out on the clinical case. The particular claim made for heroin would entail difficult and protracted work, but the issue at stake, the relief of the agony of the dying, is so important that an attempt at a controlled trial should be made. The size and nature of the list of substitutes for heroin suggested show that the kernel of the problem has been missed. These substitutes are, it is true, remarkably similar qualitatively. They all reproduce the specific actions of morphine, but there are quantitative differences in their action. For example, their relative action in depressing respiration is not proportional to their analgesic activity. There is an *a priori* reason for supposing that the claim for retaining heroin may be sound. The effect of the morphine group in alleviating pain is almost certainly not a specific annulment of the impulses transmitted through pain fibres but a cerebral action related to the sense of euphoria produced. It is just because of its outstanding euphoric effect and consequent addiction production that the use of heroin is to be abolished.

Is the social evil of heroin addiction in this country sufficiently large to outweigh the therapeutic advantage which heroin may possess? After all, the social evil of addiction to alcohol is far graver, not only in this country but in others, than addiction to narcotic drugs. The community has decided, however, that the solace the majority get from alcohol justifies the use of strict regulation rather than abolition as a means of diminishing its use by that abnormal section of the community which may become addicts.—I am, etc.,

London, N.W.1. J. TREVAN.

"Half-minute" Thermometers

SIR,—I think it is universally believed not only by the medical and nursing professions but by the entire population that when a thermometer is inscribed as "half-minute" it indicates the manufacturer's assurance that it will register the temperature of a human being in that space of time. We all know that this is not true. But we have grown up to it from the nursery, and I have no recollection of hearing a discussion as to how the manufacturers arrive at this figure or if it has any other meaning.

I heard an explanation a year or two ago which was new to me. I was told that "half-minute" had nothing to do

with registering the temperature of a human being, but guaranteed that if the thermometer were placed in warm water about blood heat it would record the temperature correctly in that time. I have asked various medical friends, but I have met no one who has confirmed this explanation. It would be interesting to know if it is correct. If so, it is astonishing that it is so little known. If it is not correct, it would be interesting to know how the "half-minute" is measured, and what it does mean.

It is certainly surprising that the medical and nursing professions have shown no curiosity as to the origin of this strange inscription.—I am, etc.,

HENRY TIDY.

London, W.8.

Diversities of Sex

SIR,—I congratulate Dr. C. N. Armstrong on his article on diversities of sex (*Journal*, May 14, p. 1173). But I would plead for the dropping of the clumsy term "pseudohermaphroditism" in favour of the compact and easily understood one of "intersex," male or female as the case may be. I do not relish the task of explaining to an intelligent parent that our scientific knowledge is such that we can class his child as a "female-false-male-female." As is shown in the article of Mr. A. F. Bromwich in your issue of February 12 (p. 395), this term of pseudohermaphroditism makes it necessary to add the prefix "true" when talking of hermaphroditism, which seems to me to add confusion to an already complicated subject.

I would also join with Mr. Michael Oldfield (*Journal*, May 28, p. 1338) in pleading that unless we are very sure of our ground we should refrain from action, either surgical or medical. There is no space to go into particular instances, but I have several ex-patients leading contented lives as adults unaware of their good fortune in not having their adrenals removed, an artificial vagina constructed, or lifelong cortisone prescribed. Finally, it is probably too much to hope that those who attend the birth of such children will refrain from giving confident and definite opinions on their sex unless they have studied the subject.—I am, etc.,

DENIS BROWNE.

London, W.1.

The Aftermath of Hysterectomy

SIR,—Dr. Winifred Coppard (*Journal*, April 2, p. 852) draws attention to the fact that some women who require hormonal treatment after hysterectomy are left without it. I, too, have met cases where serious results have thereby occurred. Reasons for the oversight are various.

(1) The patient reports to the out-patient department in six weeks. Climacteric symptoms may not yet have begun and the case is finally discharged. Or possibly a new houseman does not distinguish between climacteric and post-operative stress, so that premonitory symptoms are misinterpreted. (2) If climacteric stress occurs later, the patient may be told by her friends that this must be expected. Therefore she does not report to her doctor at all. (3) If she does report, her doctor may have received no specific instruction for post-operative treatment. Knowing that oestrogen is contraindicated in certain types of case, he may feel doubtful of giving such therapy. In any case, some practitioners are averse to the alleviation of menopausal symptoms, either because they have found the intricacies of oestrogen dosage too tiresome or because they have not experienced the trial of an exacting menopause themselves. Therefore the patient may be left with exhortation only, which can be poor comfort.

It is confusing that, although a subtotal hysterectomy should not theoretically cause an early climacteric, in fact the ovarian blood supply may be disturbed by operation and menopausal stress can start within even a few days. Again, it is not widely realized that when hysterectomy has been needed to correct conditions due to a high oestrogen balance (endometriosis, metropathia haemorrhagica, etc.) the patient will experience a far more severe hormonal imbalance than will an average woman. These are the subjects who need to take relatively large doses, even of the synthetic oestrogen preparations. It is well to remember that the presence of flushes is not an essential criterion for the diagnosis of menopausal stress. Forty per cent. of women have no menopausal flushes, yet they may suffer from severe depression or other character and functional changes during this phase.—I am, etc.,

JOAN MALLESON.

London, N.W.1.

Food-poisoning

SIR,—The article by Dr. Christopher Hardwick (*Journal*, May 14, p. 1205) on the emergency of acute food-poisoning illustrates the limitations and inadequacy of the purely clinical and therapeutic approach to a preventable condition. We must surely do something more than "recognize and treat each case as it occurs," for, unless certain steps are promptly taken, the factors causing a food-poisoning incident may continue to operate and produce many fresh victims. It is therefore to be regretted that Dr. Hardwick failed to emphasize that it is a most urgent duty of any registered medical practitioner to notify forthwith the local medical officer of health when in the course of hospital, institutional, or private practice he suspects food-poisoning in a patient. It then becomes the statutory duty of the medical officer to investigate the possible causes and to prevent further incidents by using his respective powers of detention and seizure of suspected and incriminated food. He is, moreover, armed with the legal authority to search for infectious food-handlers and to suspend them from their occupation as long as they continue to be infectious.

To assist these investigations it is of great importance that the remains of any foodstuffs consumed prior to the onset of symptoms, and any related containers, should be retained for bacteriological (and possibly also chemical) examination, instead of being destroyed as usually happens. Specimens of both vomitus and faeces should also be promptly submitted to the bacteriologist. By co-operation in these matters the practitioner first called to the patient can play a most effective part in the sphere of preventive medicine.

Certain other comments must be made. Staphylococci, usually of human derivation, may be concerned in the production of infective as well as toxic food-poisoning. Duck eggs are not merely under a cloud but should not be consumed at all unless they have been sterilized by boiling for at least 10 minutes. Lastly, your weekly publication of vital statistics shows that dysentery has been widely epidemic for many weeks and that there were 1,053 cases in England and Wales in the week ending April 23, so that familial and other outbreaks of dysentery resembling food-poisoning are far from rare, as suggested by Dr. Hardwick.—I am, etc.,

JAMES GRANT.

Gateshead, 8.

Salicylate Intoxication in Children

SIR,—We read the leading article on salicylate intoxication in children (*Journal*, May 14, p. 1201) with appreciation, except for your statement that in this country aspirin is not much used for the very young. We think, on the contrary, that it is widely and wisely used by many general practitioners and paediatricians, notably for relief of pain in teething and earache, and, furthermore, we think this is a proper use of a drug with a great margin of safety. The sleep which follows relief of pain is of benefit to the infant directly, and because his mother also is rested.—We are, etc.,

LAWRENCE PAGE.
RONALD MAC KEITH.

London, S.E.1.

Megaloblastic Anaemia of Pregnancy

SIR,—The recent important paper (*Journal*, May 21, p. 1245) from the Nuffield Department of Clinical Medicine, Oxford, is an apt reminder of the riddle of megaloblastic anaemia of pregnancy. It is indeed fortunate that, despite our ignorance of the nature of the disease, treatment is usually satisfactory. The main clinical problem is, however, early diagnosis, and it is commonly thought that the only sure method is marrow biopsy.

Recently, in a survey of anaemia of pregnancy in co-operation with Professor Fairlie and the staff of the maternity department at the Royal Infirmary, Dundee, I have been examining the buffy coat from the Wintrobe haematocrit as well as the sternal marrow. Thus far, I have found megaloblasts in the buffy coat in every case with a megaloblastic marrow. Time spent on microscopy is much less than is necessary in the examination of the ordinary blood films. The value of examination of the buffy coat in Addisonian anaemia is well known, and its application in the diagnosis of anaemia in pregnancy is one that I can fully commend.

The examination of the buffy coat from these pregnant women has revealed further points of interest. Thus erythrophagocytosis has been observed in significant degree in a number of cases. These positive findings seemed to be related either to the uterine activity of labour itself or to abdominal pain during the last few months of pregnancy, pain which might well have been due to uterine activity. The possibility that these uterine contractions forced foetal erythrocytes into the maternal circulation has already received some serological confirmation.—I am, etc.,

Dundee. H. B. GOODALL.

SIR,—I was disappointed to find in the article on megaloblastic anaemia of pregnancy by Drs. J. Badenoch, Sheila T. Callender, J. R. Evans, and A. L. Turnbull, and Professor L. J. Witts (*Journal*, May 21, p. 1245), no mention of the recurrence rate of this condition in future pregnancies. I have recently looked after a gravida-3 patient aged 26, in whom the condition occurred with each successive pregnancy. With her first child in 1949 she had a normal antenatal period and confinement, but was discovered on the tenth post-partum day to have a haemoglobin of 23% with a typical megaloblastic blood picture. She responded well to transfusion, liver injections, and folic acid. In 1953 the anaemia was detected during the antenatal period and she was maintained in good health on folic acid.

Finally she was admitted to hospital earlier this year, one week before term, in cardiac failure and with a haemoglobin of 25%. She was given immediate transfusion of three pints (1.7 l.) of packed cells, and went into labour after twenty-four hours. She had a rapid easy labour of nine hours and delivered herself spontaneously of a live child with a haemoglobin of 112%. After delivery she was found to have complete achlorhydria, but responded to folic acid 40 mg. daily, and her haemoglobin rose to 73% after three weeks.

I wish to thank Mr. A. J. Wrigley for permission to report this case.—I am, etc.,

London, S.E.1. A. O. RUSSELL.

Rauwolfia Serpentina in Psoriasis

SIR,—During the course of systematic study in an endeavour to find a satisfactory method of treating psoriasis, one line of approach led to the use of rauwolfia serpentina in this condition. The work on psoriasis was commenced ten years ago, and this brief report refers to only a small section of the study, which has embraced more than 1,000 cases. The results achieved with rauwolfia serpentina and the current interest in this drug, however, appear to justify a special communication.

Rauwolfia serpentina contains a large number of alkaloids of which many exhibit qualitative and quantitative differences in pharmacological action. Of these various effects, the two considered to be of particular importance for the treatment of psoriasis are sedation and adrenolytic action. Sedation has been found to be of value in psoriasis, and this type of effect is shown by at least two rauwolfia alkaloids, reserpine and rescinnamine. Therapy involving adrenergic inhibition emerged from the larger scheme of the main study, and it was noted that a number of alkaloids, such as ajmaline and raupin, have been reported to act as sympathicolytic agents. Certain alkaloids related to yohimbine have adrenergic blocking properties, and some of the rauwolfia compounds appear to be medullary stimulants which may be capable of counteracting any depressant effects induced by the sedative alkaloids in susceptible individuals.

The drug used in this series was the powdered whole root of rauwolfia serpentina standardized by biological assay. It was administered in the form of 50-mg. tablets, and control groups were given placebo tablets of identical appearance. Cases were unselected and all types of psoriasis were included. Thirty patients were treated with active "raudixin" tablets, and of these 15 cleared, 10 improved, 4 showed no change, and one became worse. Thus, 83% were benefited. Fourteen patients were given the placebo tablets, and of these 2 cleared, 3 improved, 9 showed no change, and none became worse. Thus, 35.7% were benefited. The dosage employed was one tablet given four times daily. No undesirable side effects were noted, and the drug was well tolerated by all patients, many of whom reported a feeling of well-being as well as symptomatic improvement.

Psoriasis has always proved difficult to treat, and any drug which can relieve the condition without inducing harmful reactions is worthy of consideration. Rauwolfia serpentina appears to be a useful adjunct in treatment, and further investigations are justified. I am indebted to Dr. G. Harvey for permission to publish these findings and to Messrs. E. R. Squibb and Sons for generous supplies of "raudixin" and placebo tablets and for their co-operation in technical matters.—I am, etc.,

Glasgow. G. LESLIE.

Cost of Treatment

SIR,—Some weeks ago, amongst my morning post, I received from a manufacturer of oxytetracycline a glossy, well-produced pamphlet summarizing the use of that drug in paediatrics. From it I learned of its use in whooping-cough, salmonella infections, etc., but the centre page, taking up one-third of the print, informed me that it was "preferred for threadworm infections (enterobiasis)." Lest this should escape my notice, detailed instructions were printed about the dosage for various ages, but, to make sure, I was exhorted to treat the whole family at the same time. As there was no indication of the cost of this treatment, I wrote to the manufacturers to inquire the price of their recommended treatment for a National Health Service patient aged 6 years. Their reply, excluding dispensing charges, varied from £3 to £3 11s. per patient per course, depending on the vehicle used for the drug.

Now, Sir, I have hitherto relied in some part upon literature from drug firms to keep me up to date with recent therapeutic advances. If, however, a firm of standing is prepared to advise busy practitioners to use preparations for relatively harmless conditions without at the same time indicating the crippling cost, then in future I shall throw all circulars into the wastepaper basket unopened. I may add that I have voiced my protest to the firm in question, but I have had no reply. I hope that shame is the cause of their silence.

In conclusion, I must add that I have ascertained that treatment of threadworms with piperazine hydrate—an exceedingly efficacious drug—is 3s. per course.—I am, etc.,

Newent, Glos. K. M. TOMLINSON.

Malignant Granuloma of the Nose

SIR,—With reference to Mr. Maxwell Ellis's article (*Journal*, May 21, p. 1251) several disease entities, all of them clinically very serious, are covered by the above title and may be confused in treatment. First of all there is a genuine malignant growth, a sarcoma or carcinoma, which may be diagnosable with the help of an adequate biopsy for morbid histology. Next comes the group of genuine granulomas, tuberculous, syphilitic, para-syphilitic, fungous, protozoal (Leishmania), coccal (synergistic gangrene), and fuso-spirillary and perhaps bacillary (Perez). The so-called "granuloma" of giant cell type associated with periarteritis

nodosa or disseminated "temporal" arteritis should be placed in a class by itself.

The only safe guide for treatment is careful diagnosis, in which the morbid histologist and the bacteriologist each have a special part to play—often a very difficult part. The genuine sarcoma or carcinoma requires an adequate biopsy, not the necrotic fragment which is so often all that comes to the morbid histologist, however keen and enlightened. The genuine granulomas also require an adequate biopsy, part of which should be examined histologically and part bacteriologically. It is important that both specimens, but particularly the bacteriological one, should be accompanied by a very full clinical description and history. Smears of the exudate may be very useful for the bacteriologist.

In England and America the condition usually diagnosed as "malignant granuloma" is an ulcerating gangrenous mass in the nasal cavities which gradually eats through soft tissue and bone in a most horrifying manner. Although clinically resembling the advance of a malignant growth, the process is actually inflammatory, the most likely infection being the micro-aerophilic streptococcus of Meleney associated with a pyogenic staphylococcus. Both these organisms should be susceptible to antibiotics, but are probably insensitive to penicillin and the more popular forms taken by this therapy.

The infecting organisms should be isolated in pure culture and tried against all available antibiotics in the hope of finding one to which they are sensitive. When found, this effective agent should be administered in very large doses.

The use of "deep" *x*-ray therapy—as recommended by Mr. Maxwell Ellis and Mr. Gilroy Glass—is most valuable. *X*-rays at one time used to be employed against large carbuncles with effect. The young growing capillaries and dividing cells of granulation tissue are disrupted by the small dose of *x*-rays, and organisms protected by the cells are laid bare to antibodies made by the patient and to circulating antibiotics. In these cases A.C.T.H. or cortisone can be very dangerous because the natural body defences are hamstrung: these remedies, however, may be very useful for the periarteritis nodosa or giant cell arteritis phase of a granuloma, but the infective or inflammatory phase is the most urgent and should be cleared up by the methods described *before* A.C.T.H. or cortisone is used for the systemic phase of the condition. I have not given any references, because Mr. Maxwell Ellis has given many in his paper and I do not wish to add unduly to the length of this note. —I am, etc.,

Epping. FRANK MARSH.

Prognosis in Cancer of Large Intestine

SIR,—I read with great interest your leading article (*Journal*, May 14, p. 1199) on this subject, especially the remark that "it is surely time the public were better informed about the early symptoms of the disease, for only thus can the main source of the delay be reduced." During the last two and a half years such education has been carried out in the "Yorkshire experiment," and an attempt has been made to assess the results statistically. Harnett[1] found that the delay in seeking advice varied with the position of the growth in the four parts of the rectum, but over 40% delayed for more than three months. Further, he stated that the three common symptoms were (1) chronic intestinal obstruction, (2) diarrhoea and/or bowel irritability, (3) discharge of blood and/or mucus, in that order.

In the Yorkshire experiment on education the symptoms emphasized were "rectal bleeding" and "changes in the bowel habit," but only the delay in cases of "bleeding" was assessed. The cases registered for this assessment were those in which cancer was proved, and those in which the complaint was rectal bleeding *whatever the cause*. It would be of little value to quote the "average delay" because the extremes were so far apart, especially in the latter category of cases not due to cancer—one man waited 40 years before seeking advice. Incidentally, the contrast in delay

TABLE I.—*Combined Non-malignant and Proved Cancer*

Duration of Delay	July to December, 1953		January to June, 1954		July to December, 1954	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
0–1 month ..	13	16·9	56	33·7	68	43·8
1–3 months ..	17	21·9	33	19·8	20	12·9
3–6 ,, ..	10	12·9	23	13·8	9	5·7
6–12 ,, ..	4	5·1	15	9·0	17	10·9
12–24 ,, ..	8	10·3	11	6·6	13	8·3
Over 2 years ..	25	32·3	28	16·8	28	18·0
Total ..	77	99·4	166	99·7	155	99·6

TABLE II.—*Proved Cancer*

Duration of Delay	July to December, 1953		January to June, 1954		July to December 1954	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
0–1 month ..	1	5·8	18	33·9	12	38·6
1–3 months ..	3	17·5	16	30·1	5	16·0
3–6 ,, ..	4	23·5	9	16·9	6	19·2
6–12 ,, ..	2	11·7	6	11·3	4	12·8
12–24 ,, ..	5	29·4	3	5·7	2	6·4
Over 2 years ..	2	11·6	1	1·8	2	6·4
Total ..	17	99·5	53	99·7	31	99·4

of reporting haematuria and rectal bleeding is remarkable—over 70% report haematuria within one month. The result to date, after two years' education, shows some improvement in the delay in reporting rectal bleeding in three six-monthly analyses. The figures collected are small, particularly during the first six months of the experiment, and in such a small population (600,000) it will be a long time before there are sufficient "proved cancers" to be of statistical importance. Nevertheless, there is an improvement in the percentage reporting rectal bleeding within the first month, 16.9% to 43.8%. This, in my opinion, justifies an investigation on a far larger scale, if the local health authorities can be persuaded to take part.—I am, etc.,

York. MALCOLM DONALDSON.

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Longitudinal Research in Child Development

SIR,—In our recent article, "A Longitudinal Research in Child Development and Some of its Problems,"[1] we stated, "This is the first study of its kind to be started in Britain." We gather that certain readers have misunderstood this statement, and we therefore wish to clarify our meaning. What was intended was to convey that the combined study, described by us, was the first of this *type* of study, the two main points being that it is planned from birth to maturity, and it is a combined psychological and physical investigation.

It is of course by no means the first longitudinal study in Britain. A longitudinal study was started in Oxford in 1944 at the Social Medicine Unit, Oxford University, and ran for ten years.[2] A study was started in 1948 at the National Children's Homes, Harpenden, under the combined direction of the Ministry of Health and the Sherrington School of Physiology, St. Thomas's Hospital, London. This very comprehensive study is in progress. Before these, there were longitudinal studies made some time ago by Lowe[3] and Fleming.[4]

It is hoped that what we intended to say will now be clear, and that our ambiguity will not have been thought discourteous to other investigators—a thing we should be most unhappy to feel.—We are, etc.,

TERENCE MOORE.
COLIN HINDLEY.
FRANK FALKNER.

London, W.C.1.

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Flat Foot

SIR,—Mr. T. T. Stamm's contention that in the flat-footed attitude the forefoot is "supinated" (*Journal*, May 21, p. 1279) is, in its context, unanswerable. However, his is an over-simplified description of flat foot, which is true only if by forefoot is meant metatarsus. In flat foot, not only is the foot pronated on the talus, but, at the mid-tarsal joint, the forefoot is pronated on the hindfoot. The navicular, cuboid, and cuneiforms are thus pronated, relative both to the leg and to the hindfoot, and the metatarsus only is inverted, at the tarso-metatarsal joints. Sometimes the medial cuneiform moves with the first metatarsal.

There is some truth, therefore, in the customary description of the forefoot as pronated, endorsed by Dr. J. McKenzie (*Journal*, April 30, p. 1068). The abduction element of pronation in flat foot is plain to see. Humphry,[1] a century ago, rightly indicated that rotation of the foot about its long axis (eversion) and rotation of the foot about a vertical axis (abduction) cannot occur independently as tarsal movements, but are always combined in the single movement which we call pronation.—I am, etc.,

London, E.C.1. E. SHEPHARD.

REFERENCE

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The Meaning of Social Medicine

SIR,—I must protest against Professor Thomas McKeown's smart aleck review of my book *The Meaning of Social Medicine* (*Journal*, March 19, p. 710). His introduction is flippant, and the rest of his brief treatment of my book is most cavalier. One is perhaps not warranted in expecting the professor to understand the meaning of social medicine, but surely simple decency would require him to treat an earnest work in a forthright and sober way.

His stuffy observation on "the recognition of a problem being mistaken for its solution," and his oh so superior query: why is it necessary to make exaggerated claims for a new subject?—reflect his own mind and have nothing to do with the substance or intent of my work. I am understandably grieved that my book, on the composition of which I worked so hard, has been so shabbily treated by your reviewer. Also, I feel that the readers of the *British Medical Journal* deserve something far better than the professor's boorish exhibit. I trust that not a few will take it upon themselves to see precisely what's what.—I am, etc.,

New York, 29. IAGO GALDSTON.

Gonorrhoea Statistics

SIR,—A pro-forma has recently been circulated to V.D. clinics by the British Co-operative Clinical Group requesting statistics of certain points in connexion with cases of gonorrhoea attending for the first time in 1954. The information required comprises occupation, race and country, sex and status of contact; whether alcohol was taken, the incidence of reinfection, precautions taken, and the marital status of patients. It seems a pity that, when so many important questions in venereology need statistical investigation, so much time is wasted on relatively unimportant matters.

The problems we would like to see elucidated by a nation-wide survey include the following: (1) The necessary period of surveillance in gonorrhoea. (2) The incidence, if any, of penicillin-resistant gonococci. (3) The sexual transmission of other infections such as non-specific urethritis and trichomonas infestation. (4) The optimum course of treatment for cases of acute syphilis—by no means agreed among venereologists. (5) The necessary period of surveillance in acute syphilis. (6) The optimum course of treatment for chronic syphilis including cerebrospinal forms. (7) Duration of treatment in latent syphilis. (8) The significance of doubtful serological tests in cases of pregnancy who have had previous treatment. (9) Clinical opinions of the comparative value of the different serological tests for syphilis and possibly also the standardization of technique throughout the country.

With problems of such magnitude requiring elucidation, it seems to us rather trivial to employ our time finding out if an attack of gonorrhoea was got from a casual acquaintance or a close friend.—We are, etc.,

GERALD H. KNIGHT,
Birmingham, 4. W. FOWLER.

Varicella with Neurological Complications

SIR,—I was interested to read Dr. M. S. Pathy's memorandum on varicella with neurological complications in an adult (*Journal*, May 28, p. 1324). In July, 1954, I was called to see a male patient of 32 years who developed severe headache, vertigo, and intractable vomiting three days after the appearance of a typical chicken-pox rash. His symptoms were so intense that he had to be removed to hospital. While in hospital he was examined by both E.N.T. and general surgeons, with negative findings. C.S.F. was reported as being normal. The headache and vertigo ceased after two weeks, but the vomiting persisted to such a degree as to give rise to anxiety regarding the patient's electrolyte balance. He was discharged from hospital on August 30, 1954, six weeks after admission, and complained of depression for the next week or two. He has remained quite well since this time.

There seems to be little doubt that this was a case of encephalitis complicating varicella.—I am, etc.,

London, N.W.6. D. S. GOLDFOOT.

Chloramphenicol

SIR,—Yet another coroner's inquest (*Daily Telegraph*, May 14, 1955) recorded a death due to aplastic anaemia following treatment with chloramphenicol. At the beginning of its clinical use the drug was considered a potential bone marrow toxin on account of its structure incorporating a nitrobenzene ring. Early in 1950 there were reports that chloramphenicol was responsible for certain blood dyscrasias. A nation-wide survey in the U.S.A.[1] covering the period 1949 to July, 1952, brought to light 55 cases of blood dyscrasia in patients treated with chloramphenicol alone; of these 44 had aplastic anaemia, causing death in 23. A further 95 cases of blood dyscrasia received chloramphenicol in addition to some other drugs, bringing the total to 150. The authors of this survey point out that the dosage regimen appeared to have little or no bearing on the development of the blood complications. This is also borne out by the case history reported in June, 1954, to the Société Française d'Hématologie by S. Tara, describing a patient who died from aplastic anaemia after treatment with only 3 g. of chloramphenicol. In this country, in 1952, the *British Medical Journal*[2] drew attention to this very grave complication of chloramphenicol therapy. A few instances of fatal aplastic anaemia were published in the same year by Hawkins and Lederer[3] and Wolman.[4] In 1953 more cases were seen over here[5] and abroad: Erslev[6] published 2 cases and reviewed 40 cases with 27 deaths collected from the literature. Koster and Groen[7] published one case of aplastic anaemia from which the patient died. A survey in Great Britain in 1954 by Hodgkinson[8] dealt with 31 hospital cases of blood dyscrasia associated with chloramphenicol: 28 had aplastic anaemia, which proved fatal in no less than 24 at the time of publication of the report. More recently Johnston[9] reported a case of chloramphenicol aplastic anaemia in a woman kept alive by transfusion of polycythaemic blood using sequestrene. I have seen last year a child who died from aplastic anaemia after prolonged treatment in a fever hospital with chloramphenicol for whooping-cough.

There is no doubt that chloramphenicol is not safe for use in routine antibiotic therapy. This antibiotic is the more dangerous because of its low threshold of toxicity and

because when bone marrow depression occurs it is usually irreversible and resistant to treatment. As there are at present antibiotics as effective and certainly less dangerous to life than chloramphenicol, I think it would be wiser to discontinue the use of chloramphenicol altogether.—I am, etc.,

London, W.10. A. I. SUCHETT-KAYE.

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8 Hodgkinson, R., *Lancet*, 1954, **1**, 285.
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Notification of Measles

SIR,—During the past month I have notified upwards of a hundred cases of measles. No doubt many other practitioners have had a similar experience. Has any useful purpose been achieved by the notification of this disease?—I am, etc.,

Feltham, Middx. G. T. RUTHERFOORD.

POINTS FROM LETTERS

Speaking Up

Dr. W. F. BENSTED-SMITH (Newton Ferrers) writes: There is one basic and infallible rule for unaided speech—speak always to the back row. The rest will then hear quite well.

Redundant Circulars

Dr. R. A. F. JACK (Bromsgrove) writes: My young family have helped me to deal with the surfeit of advertisements that daily swell my morning post. The elder two, who by now have lost all interest in opening them, content themselves with collecting the stamps and bemoan the fact that so many envelopes these days are franked. They then pass them on to the younger two, who, armed with a pair of scissors each, cut out patterns or any interesting figures or illustrations that take their fancy. They preserve all blotters for me; and all large white envelopes that can be ungummed are put aside for subsequent painting practice or for conversion into paper darts. The result is that my wife and I get an extra quarter of an hour's peace each morning, so that in one way or another we all benefit from the unremitting onslaught of the various drug houses.

Epistaxis

Mr. JULIUS FINE (Johannesburg) writes: With reference to the discussion by Mr. C. Gill-Carey on epistaxis (*Journal*, March 12, p. 662) I believe that . . . in hypertensive cases, where control cannot be obtained, the blood pressure should be deliberately lowered by adequate medication, using hypotensives, instead of waiting for exsanguination and shock, to be followed by blood transfusion. General practitioners have not the facilities to manage the patients in this manner, but otologists still plug away at the old stereotyped routine to the extreme discomfort of the patient. I have yet to find a case of anterior epistaxis where short-wave cautery has failed after removal of the emergency nasal packing. The modern treatment should be a bold attack, using plugs as a first-aid emergency only and deliberately lowering the blood pressure with medication before the body lowers it by exsanguination.

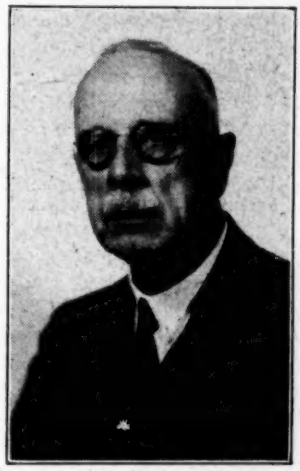
Fluoridation of Public Water Supplies

Dr. EVA HILL (Ruakaka, New Zealand) writes: The subject of fluoridation of water supplies seems to be causing a considerable controversy throughout the world. The solution of the problem requires only the use of a little common sense and intellectual honesty. . . . Fluorine is *not* essential for the development of sound teeth. No two people are alike in their response to any drugs. The proposed mass-medication is a departure from ordinary common sense that is indefensible and absurd. The dosage, being tied to water consumption, is quite incalculable. The fact that few doctors or dentists prescribe fluoride for their families or patients should cast grave doubts on the proposal to force it on everyone. Fluorine can be administered economically in accurate doses to those who are convinced of its necessity. But no man has the right to force another to take a dangerous drug against his will.

Obituary

C. W. BUCKLEY, M.D., F.R.C.P.

Dr. C. W. Buckley, of Buxton, Derbyshire, died on May 28, aged 80. He was an outstanding authority on rheumatic disease and its treatment, and his reputation extended beyond this country. By his writings and teaching and his half-century of practice in Buxton itself he did much to encourage a scientific outlook in a field of medicine where empiricism has been particularly prominent. Buxton and the Devonshire Royal Hospital, where he was senior physician for many years, owed much to him and were not slow to acknowledge the debt. When he was made an honorary freeman of Buxton in 1947 a fellow alderman declared that no one had rendered greater service to the town.



[*Navana Vandyk, London*

Charles William Buckley was born on October 10, 1874. His family had been long connected with Derby, and he held the hereditary freedom of that city by lineal descent. The greater part of his life was spent in Derbyshire, but he came to London for his medical studies at St. Mary's Hospital, where he was an entrance scholar and Kerslake scholar in pathology and bacteriology. He graduated M.B. London in 1898, and proceeded M.D. in the following year. After being house-physician at St. Mary's he worked in the fever hospital service of the old Metropolitan Asylums Board. But the early years of this century found him established in his native county and building up a reputation in the new field of rheumatology. His association as physician to the Devonshire Royal Hospital at Buxton began in 1912, and in 1917 he became a member of the management committee.

In the first world war he attended the Canadian Red Cross Hospital at Buxton, and was made honorary major of the Royal Canadian Army Medical Corps. It was as a result of his work and initiative that a large sum of money was placed at the disposal of the University of Manchester for rheumatism research, in which the Devonshire Royal Hospital assisted. By this time he had become known far beyond Buxton, and in 1923 he was elected president of the Section of Balneology and Climatology of the Royal Society of Medicine. For many years he was also associated with the Buxton and District Hospital, and among other posts which he held were those of lecturer on arthritis and chronic rheumatism to the British Postgraduate Medical School, London, examiner in hydrology to the Chartered Society of Massage and Medical Gymnastics (now the Chartered Society of Physiotherapy), and membership of the Scientific Advisory Committee of the Empire Rheumatism Council, which he did much to encourage. He became a Member of the Royal College

of Physicians in 1923 and was elected a Fellow in 1933. A life member of the Heberden Society, he was also an original member of the Association of Physicians of Great Britain and Ireland.

To the British Medical Association, to which he was first elected in 1902, Buckley gave liberal service. He was chairman of the Buxton Division in 1934–5, and president of the Derbyshire Branch in the same year. At the Annual Meeting of the Association at Eastbourne in 1931 he was a vice-president of the Section of Hydrology and Climatology, and a vice-president of the Section of Physical Medicine at the Centenary Meeting in 1932. The Association committees on which he served included the Committee on the Causes and Treatment of Arthritis, set up in 1932; the Practitioners of Physical Medicine Group Committee, of which he was a member for 18 years; and spa treatment.

In 1938 Buckley published his well-known book, *Arthritis, Fibrositis, and Gout*, and he was the author of many articles in the specialist journals and in the *Encyclopaedia of Medical Practice* and the *Index of Treatment*. In 1939 a new quarterly journal, *Annals of the Rheumatic Diseases*, made its appearance under the aegis of the Scientific Advisory Committee of the Empire Rheumatism Council. Buckley, who had been largely responsible for the annual reports of the British Committee on Chronic Rheumatic Diseases, set up by the Royal College of Physicians of London in 1934, was the obvious choice as editor; and for fourteen years, until the end of 1953, he put his great experience and knowledge into that publication—since 1944 published by the British Medical Association—so that it became known as the leading rheumatological journal of the world. For many years he was a valued contributor to the *British Medical Journal*.

Buckley never failed to take his part as one of the chief citizens of Buxton. He became a member of the urban district council in 1906, and when Buxton became a borough in 1917 he was appointed chairman of the finance and general purposes committee, a position which he held for thirty or more years. In 1923 he became one of Buxton's first aldermen, and in 1924 mayor of the borough. He took a primary part in the public inquiry and in the negotiations which preceded the acquirement by the corporation of the famous pavilion gardens. Buckley was one of the most likeable of men, although he never sought popularity. There was something about his occasional speeches, whether at the Royal Society of Medicine in London or in the council chamber at Buxton, which held the attention. No one can ever have been bored by him. His quiet manner, the dignity of his words, the occasional half-cynical wit, and above all the breadth of vision were always impressive. He married Miss Lilian Hughes, of Manchester, and had one son, who died last year, and three daughters. In his retirement he went to live at Ashbourne, still in the same county, where he could pursue his chief recreation of fly-fishing, but he continued in consulting practice and visited the Buxton clinics until his last year of life.

We are indebted to Dr. W. S. C. COPEMAN for the following appreciation: Buckley's inquisitive and critical mind and scientific outlook worked against a wider background of general medicine than was usual amongst spa practitioners in his time. He felt strongly that the study of the rheumatic group of diseases was largely in their hands, but that it had become empirical and divorced from the main current of scientific medicine. At a period when such an approach was difficult and unusual he undertook the systematic observation of these diseases as they presented themselves in his hospital and private practice in Buxton over a long period. He was thus instrumental in advancing our knowledge of certain of these diseases, more particularly ankylosing spondylitis. In this way he laid the foundation for the infant specialty of rheumatology as a branch of internal medicine. His election to the Fellowship of the Royal College of Physicians in 1933 was a signal mark of academic approbation of his work: such an award to a provincial physician in such circumstances was unusual at that time. Although the most modest of men, he continued to take active pride in this distinction all his life.

He was active also in projecting his views into the international field, mainly through the medium of the International Society of Medical Hydrology, and later the International League against Rheumatism, whose congresses he invariably attended. It was at the Rome congress in 1925 that I first met him discoursing characteristically to a small group of slightly puzzled Continental physicians on the influence of fly-fishing on the progress of British medicine—for he was a great fisherman, and firmly believed that this pursuit reconditioned the intellect as nothing else could. In spite of my very junior status he managed to have me elected as medical secretary of both bodies "to keep the trend of their activities," as he put it, "within the framework of general medicine and outside that of formal spa therapy."

Buckley was a quiet, kind, thoughtful man, with a sly sense of humour which some of his "victims" never discovered. About the time of the advent of the National Health Service he retired from the Devonshire Hospital and also from private practice; and it evidently grieved him that no appreciation of his great services to Buxton over a period of more than forty years was voiced by the new regional authority.

He was an original member of the committee of the Royal College of Physicians on chronic rheumatic diseases, which was formed in 1932 under the chairmanship of Sir Humphry Rolleston, and which four years later became the nucleus of the Empire Rheumatism Council; and he acted as editor of their "Reports," which later became the *Annals of the Rheumatic Diseases*. He resigned from this office only last year, when a special number was dedicated to him on his 80th birthday: the last time most of us saw him was at a dinner held at the Athenaeum at which Lord Horder presided, when a beautifully bound copy was presented to him. He will be much missed in many circles.

Dr. HUGH BARBER writes: C. W. Buckley made a reputation in Derbyshire in which he had no rival. He was accepted as the leading authority on "rheumatic" and allied disorders. His skill and experience were valued by the profession, and his kindly wisdom made him an excellent consultant. He was, moreover, a good general physician—of which there is proof, because more than twenty years after taking his M.D. he could satisfy the Censors of the Royal College of Physicians by passing the examination for Membership. A good committee man because he could pick out the essentials, he was a clear and concise speaker in a lecture or at a medical meeting, keeping to the point and making his meaning clear. In consultation he had the art of explaining things clearly to the patient and relatives. He was a student of medicine for more than sixty years, and in this way he kept in touch with younger colleagues when he had outlived so many of his contemporaries. Although he may have seen some of the old type of spa practice go rather out of fashion, he had sufficient work among the residents to compensate for this, and wide professional interests outside his own county which always kept him busy. He had recently been made an honorary member of the East Midland Society of Physicians, and I know he was sorry that he was not well enough to attend the last general meeting. The friendships he formed in such professional contacts were a real pleasure to him, and he will be missed by his friends and by a younger generation.

R. L. LANGDON-DOWN, M.B., M.R.C.P.

Although he had withdrawn from the central work of the British Medical Association for many years, Dr. R. L. Langdon-Down, whose death on May 29 we record with much regret, will be well remembered at Headquarters. For more than 30 years he devoted a large amount of his time to the work of the Association, retiring from active participation in 1935, when he was made a vice-president. He was in his 89th year.

Reginald Langdon Langdon-Down, who was born on August 4, 1866, was the eldest son of the late Dr. J. L. H. Langdon-Down, who founded the mental home at Teddington which his son was later to direct for many years. From Harrow School he went on to Trinity College, Cambridge, where he took his B.A. with a first-class in the Natural Sciences Tripos in 1888. He continued his clinical training at the London Hospital, and after graduating M.B., B.Chir. in 1892 he served as assistant demonstrator of anatomy and house-physician at his own teaching hospital.

In 1894 he took the M.R.C.P. and then went into private practice in the Richmond, Twickenham, and Teddington district, and in later years he also had a consulting practice in the West End. His particular bent was towards psychiatric work, especially work in mental deficiency. He became physician to the National Association for the Welfare of the Feeble-minded. When his father died in 1896 he and his brother, Percival Langdon-Down, carried on Normansfield, a home for mental defectives at Teddington. Percival died in 1925, and Reginald then took sole charge of the home until it was taken over by the National Health Service. Langdon-Down had a great gift of human sympathy. He was the kindest of men, and approached the unfortunate cases with which he was so largely occupied from a human as well as from a scientific point of view. Thus his article on "Idiocy" in *Quain's Dictionary of Medicine*, with its careful suggestions for treatment, is far more hopeful than many writings on the subject. His interest in children was by no means limited to the mentally deficient. He was occupied in all phases of child psychology and generally in the care and treatment of children. He was one of the honorary secretaries of the Section of Psychological Medicine at the Annual Meeting of the B.M.A. at Oxford in 1904 and a vice-president of the Section of Psychology at Toronto in 1906; and he represented the Association on the Child Guidance Council.

In his later years Langdon-Down was chiefly known in the Association for his work in medical ethics. He was a member of the Central Ethical Committee for a quarter of a century, and for some years was its chairman. But in his earlier career he was interested at every point in medico-political activities. When he was only 37 he had become chairman of his Division—the Richmond Division. Later he was chairman of South Middlesex Division. In 1904 he became a member of the council of the Metropolitan Counties Branch, and eventually became Branch president in 1914. He served his Division as representative at no fewer than 30 Annual Meetings. During the period 1903 (the first A.R.M.) to 1934 he was absent from the Annual Representative Meeting on only two occasions. When he became a member of the Central Council in 1917, retaining his seat until 1937, a long period of active work at the centre began. His service on the Ethical Committee was conspicuous for the patience and skill he exemplified in the very delicate matters which come before that body. His co-operation was also sought in any Association work which had to do with his own subject of psychiatry. He was the leading spirit in the preparation and submission of evidence to the Royal Commission on Lunacy Law and Mental Disorder which sat under the chairmanship of Lord Macmillan in the late 'twenties. In 1926–9 he had the difficult task of presiding over a special committee set up by the Association to consider the question of psycho-analysis. At times during those long and seemingly irreconcilable discussions on a subject of acute controversy it seemed as if the committee must throw in its hand, and that it eventually produced a useful report was due above all else to the patience, dignity, and courtesy of its chairman and his capacity for understanding widely different points of view. Another subject on which he was able to speak with authority was the law relating to patents, and he took part in conferences on that subject in 1931 and 1932. For a time he was a member of the Finance and Journal Committees. Indeed, the full list of committees on which he served would be tedious to set out, but it meant the expenditure of great energy over a long period of years and in subjects which were often of a special character, calling for unusual knowledge and experience.

Though he lived an exceedingly busy professional life Langdon-Down had many outside interests. An enthusiastic painter in water-colours, he was also an authority on Oriental porcelain. He was at one time chairman of the governors of Hampton Grammar School and a governor of Epsom College.

Langdon-Down was twice married. His first wife died in 1917. Five years later he remarried, and his second wife died in 1942. He leaves two sons and two daughters, one of whom, Lady Brain, is the wife of Sir Russell Brain, the President of the Royal College of Physicians.

R. S. FREW, M.D., F.R.C.P.

A well-known specialist in diseases of children, Dr. Robert S. Frew, formerly physician to The Hospital for Sick Children, Great Ormond Street, and since his retirement consulting physician, died at his home at Chipping Campden in Gloucestershire on May 30.

Robert Skeoch Frew was born in Newfoundland on August 22, 1881, and was educated at St. John's. For his medical training he went to the University of Edinburgh, where he graduated M.B., Ch.B. in 1905. He also studied for some time at the University of Berlin. After serving as house-physician at the Royal Infirmary, Edinburgh, and for a brief period as assistant to the professor of pathology there, Dr. Frew came to London to The Great Ormond Street Hospital, where he was medical registrar, pathologist, and clinical assistant in the out-patient department. Later he was appointed physician to the hospital, and practised also as a consultant in paediatrics in Wimpole Street. He proceeded M.D. in 1910, and in 1911 became M.R.C.P. London. He was at one time assistant physician to the East London Hospital for Children, Shadwell, and from 1914 to 1928 he was physician to the children's department, King's College Hospital, Denmark Hill. Other hospital appointments which he held for many years were those of physician to Lord Mayor Treloar Orthopaedic Hospital at Alton in Hampshire and consulting physician for diseases of children to the Bromley Cottage Hospital. During the first world war he served as major in the R.A.M.C.

Dr. Frew was an individualist in paediatrics, holding views which were not always shared by the paediatricians of his time. These he expressed particularly in his book, published in 1936, entitled *Diseases in Childhood: A Clinical Study*. The book deals solely with diseases of infants, and describes a long series of cases which had come under his personal observation. He was also the author of many articles on paediatric subjects in the general and specialist journals. One of his earliest contributions, in which he collaborated with the late Sir Archibald Garrod, consulting physician to Great Ormond Street, was on glycosuria in tuberculous meningitis. He became a Fellow of the Royal College of Physicians of London in 1919.

He leaves a widow and a daughter.

J. A. C. writes: In the sudden and unexpected death of Dr. C. A. R. McCAY (whose obituary was published on May 28, p. 1347), Oxford lost one of its oldest and best-loved family doctors. Residing and practising for over thirty years in the Headington district, he had with his sympathy and kindness endeared himself to many thousands of past and present residents of the area. Apart from being their family doctor he was their guide, counsellor, and friend, and nothing was too much trouble where his patients were concerned. His quick sense of humour, his ready smile, and his quiet understanding and attention often turned gloom and despair into hope and determination. Setting himself a very high standard in medicine and keeping himself up to date with regular reading, he was a fine example and inspiration to his younger colleagues. Apart from medicine he was a man of wide interests, among which were shooting, fishing, golf, photography, and the collection of antiques. But first of all he was a family man, and to his widow and children we tender our deepest sympathy.

Medico-Legal

LEGAL LIABILITY IN THE N.H.S.

Until recently the judiciary both in Scotland and in England shared the view held in the medical profession that doctors should unquestionably accept full and sole responsibility in law for the treatment of patients in their care. The courts held that, since hospital doctors were not in any legal sense servants of the hospital authority, the hospital authority was not vicariously responsible for the professional actions of these doctors. But a series of modern judgments in the courts of appeal in England, and latterly in Scotland, shows that judicial opinion, and thus the law, has radically altered.

For instance, Lord President Cooper in *Hayward* v. *Board of Management for Royal Infirmary of Edinburgh* (1954) said that "the old Scottish decisions . . . are no longer applicable to a fundamentally different situation. Under the new Act and regulations the obligation on the State is in my view to treat the patient and not merely to make arrangements for his treatment by and at the sole responsibility of independent contractors." And Lord Justice Denning in *Razzel* v. *Snowball* (1954), the defendant being a part-time consultant orthopaedic surgeon, gave his opinion that "whatever may have been the position of a consultant in former times, nowadays, since the National Health Service Act, 1946, the term 'consultant' does not denote a particular relationship between a doctor and a hospital. . . . Whether he is called specialist or consultant makes no difference. He, like the rest of the staff, is merely carrying out the duties of the Minister."

Hospital Doctors

The Central Consultants and Specialists Committee (Scotland) has circulated a memorandum for consideration by hospital doctors, general practitioners, and local authority medical officers in Scotland, calling attention to the present position.

The memorandum says that there is no reasonable doubt that the N.H.S. Acts, whatever their intention, have established a State hospital service in which the participating doctors are in law State servants. The whole profession should recognize a situation which raises issues of the utmost importance, particularly as doctors agreed to enter into contract with the new hospital boards principally on the assurance that there would be no significant change in their relationships with hospital authorities.

The committee does not think that hospital boards would wish deliberately to interfere with clinical discretion, but that they will be compelled to lay down rules or procedure for certain categories of medical staff in order to safeguard public funds. In support of this belief it mentions a recent action in which the court assigned the whole liability for damages to the hospital authority because it had allowed a junior medical officer to give a particular anaesthetic with unfortunate results. Apart from its intangible effect on the teaching and practice of hospital medicine, the Committee says that such a development could seriously hamper everyday hospital work, and that it could not be assumed that such a process once started could be limited.

The effect of the new relationships has already become apparent in the confidential handling of medical records. Hospital authorities require medical records and reports for legal purposes to be submitted to their own solicitor before passing them on. The Department of Health, in response to inquiry, adduces as the reason for this the responsibility of the Secretary of State and his agents, the hospital boards, "for treating patients."

Doctors Outside Hospitals

So far, the memorandum continues, the effects of these judicial interpretations of the N.H.S. Acts have been confined to the hospital field, but it would be logical to extend the doctrine of State responsibility to include treatment of patients under the Acts outside hospitals. It is doubtful if general practitioners' contracts with executive councils—"for services," not "of service"—would be sufficient to prevent it. If this happened all doctors in the N.H.S. would be servants either of the central Government or of local authorities.

Necessary Action

The Central Consultants and Specialists Committee (Scotland) has invited the Joint Consultants Committee (Scotland) to take steps to secure re-establishment in law of the previous relationship of hospital doctors to the management of the hospitals in which they work. The latter committee has received certain advice on the steps which they should take. Broadly, these will involve seeking the agreement of the United Kingdom Joint Consultants Committee to a common approach to the Government urging the necessary legislative action. Since it would be necessary for Parliament to be satisfied that any change did not infringe or diminish a patient's legal right to damages when negligence is proved, it is considered probable that governmental agreement to this action would be conditional on the profession accepting an arrangement under which membership of a medical protection society (or equivalent insurance) was a condition of employment of medical staffs in N.H.S. hospitals. The element of compulsion in such a condition is fully recognized, but the consensus of opinion of both committees is that acceptance of it is justifiable in view of the risk of much more important infringement of professional freedom if nothing is done.

To ensure that the Scottish Joint Committee knows the feeling of the profession in Scotland, meetings of hospital doctors, general practitioners, and local authority medical officers will be asked to report the numbers in favour of and against action being taken on the lines indicated in the memorandum.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 21** (No. 20) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	17	2	1	0		22	0	4	0	0
Dysentery	1,232	60	314	11	2	1,104	144	324	6	4
Encephalitis, acute	1	0		0		5	1	0	0	0
Enteric fever: Typhoid	3	0	0	0	1	3	0	0	0	0
Paratyphoid	7	1	2	0		4	0	2	0	0
Food-poisoning	150	21		6		195	20		0	
Infective enteritis or diarrhoea under 2 years				9	13				16	15
Measles*	23,655	962	160	242	285	1,940	61	187	124	329
Meningococcal infection	27	3	7	0		27	1	10	1	3
Ophthalmia neonatorum	31	1	6	0		37	3	7	0	
Pneumonia†	377	19	127	10	4	520	32	180	8	4
Poliomyelitis, acute: Paralytic	16	3	6	0		17	0	4	2	0
Non-paralytic	3	1				9	0			
Puerperal fever§	209	37	10	1		208	27	14	2	
Scarlet fever	620	43	65	37	25	832	42	115	41	32
Tuberculosis: Respiratory	812	96	153	26		933	114	155	35	
Non-respiratory	112	9	18	11		150	14	33	4	
Whooping-cough	1,613	91	114	56	28	2,419	104	352	29	25

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	0
Infective enteritis or diarrhoea under 2 years	6	0	1	0	0	9	0	1	0	1
Influenza	8	0	0	1	1	16	3	0	0	1
Measles		1	0	0	1			0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	177	16	19	15	7	179	21	17	13	4
Poliomyelitis, acute	0	0			0	0	0			
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis: Respiratory	60	6	13	0	7	83	13	12	2	7
Non-respiratory		0	1	0	6			0	1	0
Whooping-cough	1	1	0	0	0	1	0	0	0	0
Deaths 0–1 year	219	24	20	6	17	223	28	29	9	13
Deaths (excluding stillbirths)	4,955	674	572	113	174	4,734	653	591	123	155
LIVE BIRTHS	7,532	1092	937	215	412	8,243	1290	954	202	427
STILLBIRTHS	179	22	20			200	28	31		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

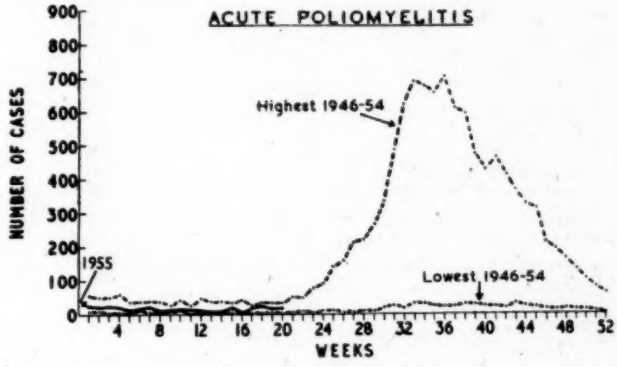
Infectious Diseases

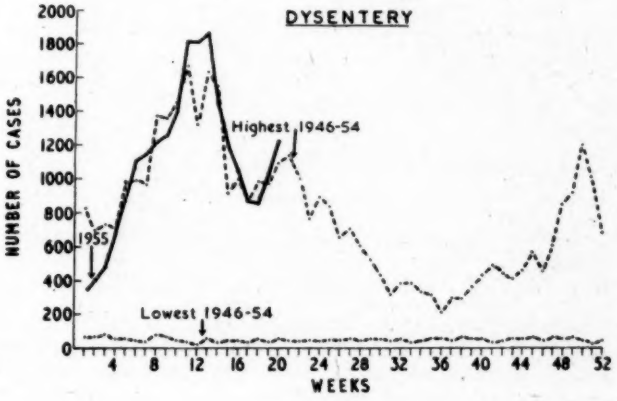
The largest variations in the number of notifications of infectious diseases in England and Wales during the week ending May 21 were increases of 3,271 for measles, from 20,384 to 23,655, 194 for dysentery, from 1,038 to 1,232, and 49 for scarlet fever, from 571 to 620, and decreases of 192 for whooping-cough, from 1,805 to 1,613, and 64 for acute pneumonia, from 441 to 377.

The largest increases in the incidence of measles were 402 in Middlesex, from 1,314 to 1,716, 332 in Southampton county, from 948 to 1,280, 331 in Kent, from 856 to 1,187, 322 in Yorkshire West Riding, from 1,867 to 2,189, and 281 in Gloucestershire, from 585 to 866; the only large exceptions to the general rise in incidence were decreases of 101 in London, from 1,063 to 962, and 94 in Staffordshire, from 1,055 to 961. The only local variation of any size in the returns of scarlet fever was a rise of 26 in Lancashire, from 74 to 100. The largest fluctuations in the trends of whooping-cough were rises of 36 in Lancashire, from 164 to 200, and 35 in Lincolnshire, from 40 to 75, and falls of 73 in Yorkshire West Riding, from 149 to 76, and 30 in Warwickshire, from 123 to 93. 17 cases of diphtheria were notified, being 8 more than in the preceding week and the largest total for 9 weeks. The chief centres of diphtheria were Liverpool C.B. 5 and Birmingham C.B. 3. The largest returns for acute poliomyelitis were London 4, Somersetshire 2, and Essex 2 (Walthamstow M.B. 2).

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





Medical News

Live Virus Reported in Cutter Vaccine.—According to the *Daily Telegraph's* New York correspondent, Professor L. P. GEBHARDT, professor of bacteriology at Utah University, has announced the recovery of live poliomyelitis virus from samples of Salk vaccine made by the Cutter Laboratories and used in the State of Idaho. Apparently only one of the three virus strains contained in the vaccine, Type I, was recovered in Professor Gebhardt's tests on monkeys. The Cutter Laboratories were one of the six firms originally supplying Salk vaccine for the mass poliomyelitis inoculations in the United States, and it was their product that was first withdrawn when cases of paralytic poliomyelitis occurred after vaccination (see *British Medical Journal*, May 7, p. 1166). The *Daily Telegraph's* correspondent also reports that court permission has been given to the parents of a child who developed poliomyelitis after vaccination to file a claim against the Cutter Laboratories. The amount claimed is stated to be £35,800.

Eighth World Health Assembly.—W.H.O.'s working budget for 1956 is to be $10,203,000. This includes $9,612,000 recommended by the Director-General, Dr. M. G. CANDAU, to finance W.H.O.'s activities, $309,484 intended for the provision of supplies and equipment to the health services of countries participating in malaria eradication campaigns, and $42,000 to launch W.H.O.'s work on the peaceful uses of atomic energy and the protection of populations against the effects of atomic radiation. A world-wide fund for the eradication of malaria is also to be set up. It will be devoted to the provision of supplies, equipment, and services to those governments whose needs cannot be met through W.H.O.'s regular and technical assistance budgets. Sudan was unanimously accepted as an associate member of W.H.O. This brings the total membership to 85, including four associate members.

Presentation to Children's Hospital of Philadelphia.—As part of the centenary celebrations at the Children's Hospital of Philadelphia, U.S.A., Professor A. A. MONCRIEFF, acting as the delegate and spokesman of the Hospital for Sick Children, Great Ormond Street, and other British paediatric hospitals, presented the American hospital with a block and gavel made from the wood of a plane tree from the garden of the Great Ormond Street hospital.

Faculty of Anaesthetists.—At a meeting of the Board of the Faculty of Anaesthetists on June 1 at the Royal College of Surgeons of England, Dr. FRANKIS T. EVANS (St. Bartholomew's Hospital) was elected dean and Dr. R. F. WOOLMER (Royal Infirmary, Bristol) was re-elected vice-dean for the ensuing year.

COMING EVENTS

Maternal and Child Welfare.—Annual conference of the National Association for Maternal and Child Welfare on June 22–24, at Church House, Westminster. Opening by Minister of Health. Particulars from the Secretary, N.A.M.C.W., Tavistock House North, Tavistock Square, London, W.C.1.

West London Medico-Chirurgical Society. — Annual banquet on June 23 at the Royal College of Surgeons.

Cambridge Graduates' Medical Club.—Annual general meeting and dinner at Jesus College on June 24. Details from Dr. T. B. ANDERSON, 1, Huntingdon Road, Cambridge.

G.P. Refresher Course at Bristol.—There are still vacancies in the course from July 11 to 16. Applications to Dr. A. H. GALE, director of medical postgraduate studies, the University, Clifton, Bristol, 8.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, June 11

NORTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Rochford General Hospital, 12 noon, Dr. E. G. Sita Lumsden: Pulmonary Tuberculosis and Diabetes Mellitus; 2.30 p.m., Dr. R. J. Powell: Ototoxic Effects of Streptomycin and Dihydrostreptomycin; 3 p.m., Mr. D. S. M. Barlow: Constrictive Pericarditis.

Tuesday, June 14

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Serology and Laboratory Diagnosis of Syphilis.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—12 noon, Dr. W. G. Oakley: Diabetes and Pregnancy.

●MIDDLESEX HOSPITAL.—4.30 p.m., Sanderson-Wells Lecture by Professor R. A. McCance, F.R.S.: Old Thoughts and New Work on Breads White and Brown.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor W. J. Atkinson: Early Management of Head Injuries.

Wednesday, June 15

HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., Dr. H. J. Shorvon: Use of Drugs in the Induction of the Hypnotic State.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Cutaneous Manifestations of Syphilis.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. G. Simon: Some Pitfalls in Chest Radiology.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—4.30 p.m., Mr. A. Goodwin: Wertheim's Hysterectomy.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., annual general meeting. Address by Sir William MacArthur: An Account of Some of Sir David Bruce's Researches, Based on his own Manuscript Notes.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. P. H. Tooley: Lecture-demonstration in psychiatry.

Thursday, June 16

INSTITUTE OF CARDIOLOGY.—11 a.m., Dr. Lewis Dexter (Boston): Selection of Cases for Cardiac Surgery.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Basal Cell Epithelioma.

INSTITUTE OF DISEASES OF THE CHEST.—5.30 p.m., Dr. P. V. Benjamin: Programmes for Tuberculosis Control in India.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., annual general meeting and short papers by general practitioners.

OSLER CLUB OF LONDON.—At University College, W.C., 8 p.m., joint meeting with University College Medical Society in honour of Stephen Paget (July 17, 1855-1926). Professor G. P. Crowden, D.Sc.: Some Pioneers in Experimental Physiology; Dr. J. H. Baron: The Brown Dog of University College.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. I. C. Gilliland: Exophthalmos.

ROYAL SOCIETY.—4.30 p.m., Croonian Lecture by Professor C. H. Best, F.R.S. (Toronto): Dietary Factors in the Protection of the Liver, Kidneys, Heart, and Other Organs in Experimental Animals—The Lipotropic Agents.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration in neurology.

Friday, June 17

INSTITUTE OF CARDIOLOGY.—At Barnes Hall, Royal Society of Medicine, 5 p.m., St. Cyres Lecture by Dr. Lewis Dexter (Boston, U.S.A.): Atrial Septal Defect.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. A. D. Porter: Light Sensitivity.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. G. Scadding.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. W. D. Doey: Sinusitis and Chest Disease.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. A. C. Thackray: Mucous Gland Tumours.

Saturday, June 18

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, Oxford University, 11 a.m., 341st meeting. Scientific papers.

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Benenden Sanatorium, 10.30 for 11 a.m., address by Professor H. Trimble (California), followed by a clinical demonstration by Dr. A. L. R. Mayer and his staff: Carcinoma of the Lung as a Differential Diagnosis of Pulmonary Tuberculosis.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Barnes.—On May 30, 1955, at St. Helen's Hospital, Barnsley, Yorks, to Mary, wife of Roy Barnes, M.R.C.S., L.R.C.P., D.P.H., a daughter—Cyrena.

Beveridge.—On June 2, 1955, at Haywood Maternity Hospital, Stoke-on-Trent, to Cynthea, wife of Dr. T. S. Beveridge, a son—Anthony Michael.

Day.—On May 21, 1955, to Micky, wife of Michael H. Day, M.B., B.S., a son—Jeremy Paul.

Goodson.—On June 2, 1955, at Tacoma, Washington, U.S.A., to Leonora (formerly Taylor), and Michael P. Goodson, M.D., a daughter—Sarah.

McCallum.—On June 4, 1955, to Dr. and Mrs. D. I. McCallum (Dr. Isabel S. Smellie), of 27, Magdala Road, Mapperley Park, Nottingham, a daughter.

Sers.—On May 12, 1955, in Antigonish, Nova Scotia, to Dr. Phyllis Mary (formerly Neil), wife of Dr. Rolf Sers, a sister for Robert—Larissa Anne.

DEATHS

Fothergill.—On May 6, 1955, at "Hensol," Chorley Wood, Herts, Claud Francis Fothergill, M.B., B.Ch., aged 77.

Vallance.—On April 21, 1955, at Woodend Hospital, Aberdeen, James Vallance, *M.C.*, M.B., Ch.B., of Flebister, Sanday, Orkney.

Vaughan.—On April 28, 1955, at Shrubland, Norwich Road, Wymondham, Norfolk, Arthur Llewellyn Vaughan, M.R.C.S., L.R.C.P., late of Diss, Norfolk, and Great Yeldham, Essex, aged 81.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

How Early can Mongolism be Diagnosed?

Q.—*I shall be grateful if you would let me know what is the earliest age at which a child can be diagnosed as suffering from mongolism, and whether the condition can be diagnosed radiologically before the child is born.*

A.—Mongolism can be diagnosed at birth, although it is by no means always possible to be sure of the diagnosis during the first days or even weeks of life. Except in the most typical instances, therefore, it is wise to suspend judgment until it has been possible to assess all the signs most carefully. Mongolism is essentially a condition in which mental deficiency is associated with a number of other congenital abnormalities, which commonly occur together in mongolism but any of which may be found in the normal. It is thus easy to be mistaken if a normal child shows some of the features of mongolism, especially in the first days of life.

The shape of the skull is very constantly abnormal in mongolism, and it is possible that the flattened occiput could be recognized radiologically before birth. On the other hand, this flattening of the occiput may be seen in the normal and be absent in the mongol. An observation that a child's skull *in utero* was an abnormal shape might legitimately arouse some suspicion of mongolism, but no more than that.

Clothing for Children in Hot Climates

Q.—*In this relatively hot climate I advise mothers to dress their children in one layer of clothes only, preferably of "cellular" weave, so as to protect the child from the sun while at the same time allowing free circulation of air and evaporation of sweat. I condemn tight vests or layers of clothing of any form, especially during the rains, as this would lead to the formation of a moisture-soaked airlock between the garments and discourage the action of the skin. Is this advice sound?*

A.—The only clothing required by a resting child when the ambient temperature is above 84° F. (28.9° C.) and he is sheltered from the wind is that dictated by decency; for an active child the limit will be lower. At temperatures below this, or when there is a breeze blowing on the body, first the skin and then later the whole body cools; hence the importance of seeing children are properly covered at night. Garments in a cellular weave when worn on the outside or as the sole garment are not demonstrably cooler, in experiments, than are other types, provided the cloth is no thicker; in general the thermal insulation of any cloth, of whatever weave, is proportional to its thickness, and cellular material, because of the way it is woven, is often thicker than other cloth of the same weight. For cellular material to be really cool when worn as an outer garment or in contact, through, for example, unzippered vents in a wind-breaker, with the outside air, the cells must be large in diameter, as in the Norwegian *brinje* garments.

The "moisture-soaked airlock" between two layers of clothing is only a reality when the outer layer is waterproof, or at least water-repellent; but if there is a lot of sweating and not much evaporation the fewer layers the better, and the advice your questioner gives to mothers is therefore good. He is also right to condemn tight vests; loose-fitting clothes are preferable, because there is then better pumping action between the clothes and the skin, giving more flow of air over the skin. Protection from the sun is certainly necessary; first, to avoid upsetting the heat balance—solar radiation on the body can impose a heat load equal to the metabolic heat load of walking; and, second, to avoid sunburn. Your questioner might be interested in the dictum reputed to have been pronounced by the late Sir Charles Martin: "The rational dress for the Tropics consists of a sunshade and a pair of sandals only."

Chrome Ulceration

Q.—*What is the latest treatment for chrome ulceration on the skin and eyes?*

A.—It is assumed that appropriate preventive measures have been applied in the process concerned, and that personal protective measures are observed. Chrome ulceration can be prevented by covering any skin abrasion immediately with a waterproof dressing so that dust, mist, or solutions of chrome compounds cannot come in contact with damaged skin. No specific treatment is known for the ulcers, which heal slowly. The lesions should be inspected daily and care taken to avoid secondary infection.

The safest and most effective first-aid treatment following contamination of the eyes is adequate washing of the eyes with water. This should be started immediately and continued for at least twenty minutes. Except for the relief of pain, if necessary, by the insertion of homatropine and cocaine drops, or cocaine lamellae, no further treatment should be given until expert ophthalmological advice has been obtained.

Stewed Fruit and the Diet in Rheumatism

Q.—*Are stewed fruits, cooked with sugar, unsuitable for "rheumatic" subjects, and, if so, why?*

A.—There is no evidence to suggest that stewed fruits cooked with or without sugar are unsuitable for "rheumatic" subjects.

Dietary restrictions are generally not required in rheumatic disease, but obese patients may be encouraged to lose weight through a restricted calorie intake, since in this way damaged joints can be relieved of an unnecessary load.

Racial Differences in Runners

Q.—*(1) A friend who is keenly interested in athletics tells me that he has heard it said that a narrow pelvis is an advantage to a sprinter. Is there any mechanical reason why this should be so? I should also like to know whether anthropomorphic surveys have shown a tendency for the pelvis in the black races to be narrower than in white races, which might account for the greater number of record-breaking sprinters found among the blacks. (2) I have also been told that exceptionally slow heart action is advantageous to the long-distance runner and that this is commoner among the inhabitants of cold climates, and hence the success of many Scandinavians in long-distance contests.*

A.—It is incorrect to say that any single skeletal factor is advantageous to sprinters. The pelvic shape and size may be significant, but so also is the angle between the neck and shaft of the femur, the obliquity and length of the femora, and many other morphological factors. In surveys of the relationship between bicristal measurements and mean annual temperature Roberts[1] has shown that there is a tendency for the pelvis in black races to be narrower than in white races:

Bicristal Figures (as Percentage of Stature)

French, 16.9, 16.8; Norman, 16.4; West African, 15.1, 14.5, 15.2, 14.9; Central African, 14.5, 14.2, 15.6.

It is interesting that the growth rate of first-generation European children living in tropical climates falls approximately midway between that of indigenous European and indigenous African children. This suggests that environmental factors are in part responsible for observed "racial" differences in functional and anatomical measures.

(2) Inhabitants of cold climates do exhibit slower pulse rates than those of hot climates,[2] but the differences are only evident under basal conditions :

Relationship Between Basal Pulse Rate and Mean Annual Temperature

Cold Climates.—N. American Indians, 53 per minute; Mukden (Manchuria), 53 per minute; Miao (China, high altitude), 55 per minute; Peking, 61 per minute.

Hot Climates.—Javanese, 67 per minute; Hong Kong, 64 per minute; Bengal, 67 per minute; Australia (aborigines), 65 per minute.

An athlete is not a good long-distance runner simply because he has an exceptionally slow heart action. More often the converse is true, the slow heart rate being the result of prolonged athletic training. Athletic bradycardia is not confined to runners, but is frequently found in persons subjected to almost any form of strenuous physical conditioning, and is particularly marked in marathon runners and weight-lifters.[3] Quantitative differences in training, and age differences, also play a part in the retardation of pulse frequency. Long-distance and marathon runners are usually older men with greater athletic experience than sprinters and middle-distance runners.[4]

It is unlikely that the success of Scandinavians in long-distance contests can be explained by "racial" bradycardia, and it is doubtful whether the heart action of Scandinavian runners is any slower than that of well-trained runners of any race. A more likely explanation is that a bigger proportion of Scandinavians train specifically for the long-distance events, and have consequently evolved training techniques superior to those of their rivals in countries where long-distance running is less popular. The importance to athletic achievement of improved training techniques and psychological factors has recently been stressed in this *Journal*,[5 6] and must not be overlooked when trying to assess the value of natural anatomical and physiological advantages.

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1 Roberts, D. F., "The Geographical Distribution of the Physical Characters of Man." Thesis in the Bodleian Library, Oxford. 1953.
2 —— *Actes du IV Congrès International des Sciences Anthropologiques et Ethnologiques*, 1952, **1**, 145.
3 MacQueen, I. J., unpublished data.
4 Cotton, F. S., *J. Physiol.*, 1932, **76**, 39.
5 MacQueen, I. J., *British Medical Journal*, 1954, **2**, 1193.
6 Ibid., 1954, **1**, 1143.

Inheritance of Marble Bone Disease

Q.—*The only child by the second marriage of a patient of mine has just died at 4½ months from Albers-Schönberg's marble bone disease. There is a normal child by the first marriage. How shall I advise my patient on the possibility of future children by the present marriage being affected?*

A.—The severe form of marble bone disease (usually causing death in childhood from anaemia or infection) is very probably due to a recessive gene. Milder forms, in many instances at least, are due to a dominant gene. Accordingly, if the parents are normal and the child was severely affected, as her death at 4½ months suggests, the advice to give the mother is that the risk of any future child of this marriage being affected is 1 in 4.

Possible Benefits of Removing Nicotine from Tobacco

Q.—*(1) In what form is nicotine present in tobacco? Is it possible to remove the nicotine without altering the tobacco's flavour for smoking? (2) What are the medical benefits of so doing?*

A.—(1) Nicotine is present in fresh tobacco leaf together with the minor alkaloids as soluble salts in the leaf sap, especially in the cell vacuoles. During curing and fermentation most of the nicotine is lost, passing into a mixture of pyridine compounds largely unidentified. Tobacco leaf from which nicotine has been removed can still be smoked with satisfaction by some people but not by others. The heavier smokers miss the nicotine.

(2) The factor in tobacco which is responsible for some cases of lung cancer and coronary thrombosis has not yet been established. It is unlikely that nicotine has anything to do with the production of the first of these diseases, but it may well be a responsible factor in the second. If this is so, one could hope for an improved prognosis in some cases of angina pectoris and coronary thrombosis if it were possible to provide cigarettes which contained no nicotine. Removal of nicotine would, of course, eliminate the rare danger of amblyopia.

Hazards of Thorium X

Q.—*Is there any risk in the frequent and long-continued use of thorium X varnish or ointment?*

A.—Preparations of thorium X produce very superficial reactions in the skin, when applied to its surface, by the action of the alpha particles. Theoretically these are almost entirely obstructed by the thinnest of tissue paper and one would not expect any permanent damage to the epidermis, or especially the dermis. However, traces of beta and gamma rays have been observed in the dermis and it is evident that some of the radioactive material penetrates via the sweat and sebaceous glands. Sufficient time has elapsed since the introduction of this method of treatment to justify the dogmatic statement that the risk to a patient is negligible if not more than 20 applications of thorium X in a strength not exceeding 2,000 electrostatic units per ml. or gramme are applied at monthly intervals. In some clinics many more treatments have been given when the patient accepts the risk, and so far evidence of permanent damage to the skin is rarely found. As a guide in practice one might state that unless encouraging progress has been obtained at the end of 20 paintings at monthly intervals there is little further to be expected from this treatment.

NOTES AND COMMENTS

Nausea after Morphine.—Dr. P. W. NATHAN (London, W.C.1) writes: In answering a question on the best way of dealing with nausea and vomiting following the administration of morphine ("Any Questions?" May 7, p. 1169) your expert referred to an article[1] by myself. Since I wrote that article, chlorpromazine has become available. My experience in using this drug has been limited, but it is consistent. It is clear that this drug is most useful in stopping nausea and vomiting caused by many analgesics. I have found that 25 mg. twice daily is usually enough for this purpose; I have never had to give more than 25 mg. three times a day. This drug is said to potentiate the action of analgesics, and thus there is another advantage in using it. I hope that this information will be useful to any doctors who look after dying patients with severe pain.

REFERENCE

1 *British Medical Journal*, 1952, **2**, 903.

Correction.—In the article on the "Treatment of Severe Asthma," by Dr. Margaret Macpherson (May 21, p. 1269), the dose of A.C.T.H. and cortisone during the first 24 hours of treatment should have been stated as 100 mg. (not 100 g. as printed).

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